DIFFUSE LESIONS OF THE STOMACH

An Account with Special Reference to the Value of Gastric Biopsy

BY

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TO

F M BURNET, F R S

WHO OFTEN TOLD US THAT
NEW KNOWLEDGE FOLLOWED CLOSELY
IN THE WAKE OF A
NEW TECHNIQUE

CONTENTS

PREFACE

In 1946 our Clinical Research Unit was formed by Sir Macfarlane Burnet F R S Director of the Walter and Eliza Hall Institute to work in the Institute and in the wards of the Royal Melbourne Hospital Diseases of the gastro intestinal tract were chosen for study and we soon encountered middle aged or elderly patients who had suffered from flatulent dyspepsia for many years They exhibited diffuse epigastric tenderness and an absence of the usual causes of dyspepsia such as ulcer cancer gallstones and pancreatitis We first studied the gastric secretions and found them to be depleted and in 1948 we developed the technique of gastric biopsy using a flexible gastric biopsy tube designed in the unit (Wood Doig Motteram and Hughes 1949)

Now some 10 years after our study began we are privileged to present our collected observations in this book Much of the data has been selected from our published papers which have appeared in Australia England and the United States of America We have added a limited number of observations made by other workers in this field many of whom have generously helped us over the years Our special thanks are due to Dr Avery Jones and Professor Magnus in England Dr Walter Palmer and Lieutenant Colonel Eddy Palmer in the United States of America and in Australia to members of the Medical Staff of the Royal Melbourne Hospital particularly Dr W E King Mr J O Smith Mr Grayton Brown Dr E Graeme Robertson Dr D C Cowling and finally and most gratefully to our many colleagues who have worked in our Clinical Research Unit over the years particularly Dr R Doig Dr S Weiden Dr R Motteram Dr J Funder Dr E Finckh Dr R Joske and Dr I Mackay together with their technical assistants Miss E Davis and Miss E Earle Mr E Matthaei of the Melbourne University and Mr R Ingles of the Royal Melbourne Hospital kindly helped with the photography

The title *Diffuse Lesions of the Stomach* has been u ed to include diffuse gastritis in its acute and chronic forms gastric atrophy and that rare disease diffuse giant hypertrophic gastritis It naturally includes pernicious anaemia and excludes the localised lesions of

peptic ulcer and cancer although some reference is made to their relationship to gastritis

All the studies have been undertaken in adults as no children are treated in the Hospital It may well be that some of the lesions seen in adult life have begun during childhood or even in the prenatal period

CHAPTER 1

METHODS OF INVESTIGATION

Problems of the early investigators

For many centuries physicians considered dyspepsia was frequently caused by diffuse inflammation of the stomach The celebrated Broussais (1831) initiated widespread belief in the occurrence of chronic phlegmasiae or inflammations of the stomach by reporting observations which he made while military surgeon to the army of Napoleon

However many factors confused early investigators in this field especially their failure to appreciate the gross changes which took place in the gastric mucosa soon after death In later years recourse was made to the study of specimens obtained at surgical operation but even here considerable changes were found to be brought about by the manipulations by the surgeon An appreciation of these problems created a wave of disbelief in the prevalence of gastritis especially in its chronic stage Moreover even when physicians did accept its presence they were loath to accept it as a cause of chronic dyspepsia

A challenge to this disbelief came at the turn of the present century led by the splendid studies of Faber (1935) who prevented post mortem digestion of the gastric mucosa by introducing formalin immediately after death But this post mortem material could still be criticised on the grounds that structural abnormalities might first appear during the terminal illness (see Chapter 3)

There was an urgent need for fresh undamaged specimens of gastric mucosa which could be placed immediately in a fixative solution and prepared for histological examination Moreover it would be of considerable value if these specimens were obtained with minimal discomfort and risk to the patient for this would enable a comprehensive study to be made not only in health and disease but also over a number of years in the same individual

It is our sincere belief that the technique of gastric biopsy first

described in our Unit in 1949 has made a liberal contribution to this urgent need

In this chapter the methods used in our studies are discussed

Symptomatology and clinical investigation

In addition to the history and physical examination it may be necessary to employ a fractional test meal X ray by barium meal and even gastroscopy and gastric biopsy to establish the diagnosis of gastritis and exclude other diseases with similar clinical features

Clinical history The taking of a comprehensive history is of considerable importance It may call for much time and patience from the physician but the information is rewarding The family history social history and the nature of past illnesses may be of value

In taking the history and making the physical examination it should be constantly recalled that diffuse lesions of the stomach have to be differentiated from gastric and duodenal ulcer cancer of the stomach chronic pancreatitis and other diseases involving the upper portion of the abdomen Pure functional dyspepsia will always present a problem in diagnosis often true gastritis is present with considerable functional overlay

Pain and discomfort The nature site and duration of the discomfort should be ascertained together with its provocation by food physical exertion or mental stress The type of food which causes pain is of interest—pickles pastry and sherry are often incriminated The relief of pain by alkalis dilute hydrochloric acid or food should be ascertained

Diet The appetite and the quality and quantity of the food consumed should be recorded together with the general eating habits In Australia as indeed in many other parts of the world the consumption of alcohol is often excessive and this may cause gastric disturbances due either to its direct effect on the gastric mucosa or to its influence on the diet

Physical examination In carrying out the general physical examination the local signs of gastric disease should be noted and also a special search should be made for lesions elsewhere in the body which may be associated with gastritis as they may share in a common aetiology Thus hepatomegaly and peripheral neuritis may suggest alcoholism and malnutrition

There may be premature greying of the hair atrophy of the tongue recurrent stomatitis haemorrhagic gums carious teeth or complete dental extraction anaemia purpura pigmentation or vascular spiders in the skin cardiac enlargement and tachycardia from vitamin deficiency and finally peripheral neuritis or early signs of subacute combined degeneration of the cord

Examination of the upper abdomen may reveal the diffuse epigastric tenderness of gastritis in contrast to the more local tenderness of peptic ulcer gall bladder disease or perhaps cancer A mass in the epigastrium may be hepatic enlargement hydatid disease or cancer of the stomach Rarely it may be a tumour of the body of the pancreas or enlargement of the retroperitoneal glands A more laterally placed mass may be caused by a palpable gall bladder splenic enlargement or a renal tumour

Test meal examination

The histamine test meal is a most satisfactory method of determining gastric secretion and thereby obtaining some evidence a to the state of the gastric mucosa There is good correlation between the test meal and the findings at gastric biopsy as is clearly shown in fig 1 (Wood *et al* 1949 Joske *et al* 1955) (see Chapter 5)

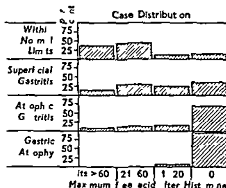


Fig 1 *The elationsl ip b tt een tl e findin s on gastric biopsy and tl I i tamine test m al* With the in r a e n the inflammatory r action and atrophy of the gastric mucosa there is a cor esponding fall n the secret on of acid There were 275 biopsi s within normal lim ts 296 showing supe ficial gastrit 172 atroph c gastritis and 41 gastric atrophy (Data from Joske Finckh and Wood 1955)

In most of our series a standard subcutaneous dose of 0 9 mg of histamine acid phosphate was used This stimulus produced a satisfactory rise in acid in normal controls and high levels in cases

of duodenal ulcer, but without producing unpleasant histamine effects in the patient Before giving histamine the stomach was emptied by passing a fine stomach tube such as the Rehfuss model, and then after giving histamine it was emptied at half hourly intervals for one and a half hours In some cases of sus pected pernicious anaemia the maximum secretory response was evoked by Kay s method (1953) when an antihistamine drug was given to counter the general systemic effects of a liberal dose of histamine (0 4 mg histamine acid phosphate per 10 kg body weight) as the antihistamine drugs do not inhibit the histamine stimulus to gastric secretion

Hypoglycaemia caused by intravenous insulin stimulates gastric secretion by way of the vagus nerve and an insulin test meal (insulin 15 units intravenously) is of value after vagotomy to assess the degree of completeness of the nerve section

An overnight test meal reveals the resting secretion over a long period continuous gentle suction or 2 hourly aspiration being used

The tubeless test meal in which the excretion of uropepsin is estimated after histamine stimulation has not been used in this series as it is less accurate than the direct measurement of gastric secretion (Levy and Levine 1956) however it is of value as a screening test for lowered gastric secretion The plasma pepsinogen level may be a guide to gastric secretion Hoar and Browning (1956) claim that it is superior to urinary pepsinogen determination

A tubeless test meal using cation exchange resins may also be used as a screening test for anacidity (Rechtschaffen and Wein garten 1957)

Radiology

The radiological examination is of considerable value in the diagnosis of localised lesions of the stomach and duodenum notably peptic ulcer cancer diverticulum and prolapse of gastric mucosa through the pylorus However the value of radiology in detecting diffuse lesions of the stomach is mostly confined to the rare disease diffuse giant hypertrophic gastritis (see Chapter 4) It is of little value as a method of detecting chronic atrophic gastritis or gastric atrophy (Joske *et al* 1955) Furthermore in our experience the diagnosis of hypertrophic gastritis based on the findings of pronounced gastric rugae has been proved by

biopsy to be incorrect except in diffuse giant hypertrophic gastritis After considerable experience Eddy Palmer (1954) has reached a somewhat similar opinion to that held in our unit

Gastroscopy

Most patients in our series were examined by gastroscopy The technique consists of spraying the throat with local anaesthetic (cocaine 1.5 ml of 3 per cent with adrenalin 1 10 000) preceded by basal sedation with chlorpromazine 50 mg omnopon 20 mg and hyoscine 0.4 mg The stomach is emptied by gravity using a large bore stomach tube and elevating the foot of the examination couch

The Hermon Taylor gastroscope was used in 95 per cent of our last 200 gastroscopies as it has a controllable lower segment which affords a good view of most localised lesions However in elderly patients especially in females over the age of 60 the less bulky Cameron model (Schindler design) was used to reduce the hazard of pharyngeal or oesophageal perforation We encountered only one such perforation in 661 gastroscopies The patient recovered after drainage of a paraoesophageal abscess which developed in spite of vigorous treatment with antibiotics Katz *et al* (1956) described a massive pneumoperitoneum after gastroscopy This subsided with conservative treatment

Gastroscopy may show congestion mucopurulent exudate and some petechial haemorrhages and even erosions in acute gastritis and during the acute relapses in chronic gastritis In pernicious anaemia with gastric atrophy the atrophy may be observed in the body of the stomach especially in the upper segments where the underlying veins are revealed

However gastric biopsy has provided evidence that gastroscopy often fails to determine whether chronic gastritis is present Thus Joske *et al* (1955) reviewed 258 instances where gastric biopsy had been performed within 2 weeks of the gastroscopy often at the same time In 164 instances where gastroscopy reported the gastric mucosa to be normal gastric biopsy revealed normal gastric mucosa in only 87 instances whereas superficial gastritis was present in 56 atrophic gastritis in 16 and gastric atrophy in 5 Although these findings could be partly due to a sampling error in the gastric biopsies the study does emphasise the limitations of gastroscopy as a method of diagnosing chronic gastritis

Gastric biopsy

In 1948 one of us (I J W) observed that fragments of gastric mucosa of sufficient size for microscopic examination might be obtained during a histamine test meal when vigorous suction was exerted through the stomach tube during the collection of the gastric juice Moreover it was found that better fragments were obtained when negative pressure was exerted and then the tube was suddenly jerked out so as to dislodge a fragment These fragments could be fixed immediately in formalin embedded in paraffin cut and stained However they contained mostly superficial epithelium

Our initial observation was subsequently found to have been recorded by Einhorn in 1894 and later by Hawksley in 1939 who subsequently heard of Einhorn s classical observation (Hawksley and Cooray 1948)

The development of the flexible gastric biopsy tube Our findings of such fragments stimulated the development in our unit of the flexible gastric biopsy tube which now has been used by the unit in carrying out 1736 successful biopsies It has also been used in its present or a modified form by other workers in many parts of the world notably by E D Palmer (1950) in the United States of America who has made many excellent contributions to the knowledge of gastric histopathology

Others who have made valuable studies with this biopsy technique either in the form described or with a modified model include Badenoch and Richards (1953) Rubins *et al* (1953) Coghill and Williams (1955) Edwards and Edwards (1956) Markson and Davidson (1956) and Shiner and Doniach (1957)

Chevalier Jackson and gastric biopsy The credit must be given to Chevalier Jackson the doyen of endoscopists for first using gastric biopsy under direct vision and establishing it as a valuable and safe method of investigating diseases of the stomach In 1906 he first performed gastric biopsy using forceps through his rigid oesophagoscope and later stated In malignant diseases a specimen may be taken with little risk in fungating conditions but in flat ulcerations suspected of malignancy the biting out of the edge of the ulcer though very easy of accomplishment is unjustifiable (Jackson 1907) His work proved of considerable value and in 1935 he and his son reported The taking of tissue through the open tube gastroscope is easily done and hundreds of cases without a single complication have demonstrated its freedom from

danger when done with proper precautions (Jackson and Jackson 1935)

In 1937 Schindler described the flexible gastroscope a momentous discovery in the field of gastroenterology Later Hermon Taylor designed a gastroscope with a controllable lower segment which afforded the operator a more extensive view of the stomach Schindler s discovery led to the development of the operating gastroscope containing a channel through which forceps can be manipulated under direct vision Now many but by no means all of the technical difficulties have been overcome following the researches in the United States of America by Kenamore (1940) Kenamore Scheff and Womack (1946) Benedict (1948) and Tomenius (195-)

Most of our studies described in this book were made with our flexible gastric biopsy tube the Hermon Taylor gastroscope or the Benedict operating gastroscope

Each instrument has its own particular virtues and limitations For diffuse lesions of the stomach the flexible gastric biopsy tube obtains one or two satisfactory fragments of gastric mucosa with minimal inconvenience to the patient In contrast to this the Benedict operating gastroscope is more bulky and may cause considerable discomfort during and after the examination However it enables fragments of mucosa to be obtained under direct vision from most parts of the stomach although fragments from antral lesions are difficult to obtain This type of instrument is thus essential for obtaining tissue from local lesions such as ulcer or carcinoma We have used the Benedict operating gastroscope on 53 occasions after preliminary inspection with the Hermon Taylor instrument Successful biopsies were obtained on 40 occasions and there were no complications

Technique of gastric biopsy with the flexible gastric biopsy tube

The technique of gastric biopsy using the flexible gastric biopsy tube designed in our unit is described in detail as this method is most suitable for studying diffuse lesions of the stomach This procedure has been the *piece de resistance* of our work

The examination can be made on out patients so long as they are not unduly debilitated or anaemic

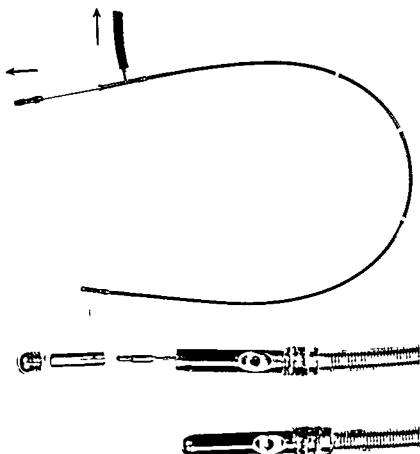


Fig 2 *Flexible gastric biopsy tube*

Top illustration The complete biopsy tube with operating handle and wire (top left) lateral tube leading to an exhaust pump (top) length of tube with white marks at levels I II and III and the operating head (lower) (By ¹)

Centre illustration Operating head with terminal screw (left) removed allowing the cylindrical blade to be thrust down and unscrewed from the operating tube This enables the biopsy fragment to be obtained (× 1½)

Lower illustration Operating head assembled The cutting edge of the cylindrical knife blade is visible through the lateral hole (× 1½)

biopsy tube consists of a length of coiled Bowden wire covered by plastic tubing to render it airtight (fig 2) (Wood *et al* 1949A and B Doig and Wood 1952) * At the lower end a steel cylinder is attached which houses a cylindrical knife blade with a proximal cutting edge The end of the cylinder is closed with a terminal screw and its side is pierced by a countersunk circular lateral hole $\frac{3}{32}$ inch in diameter through which a fragment of gastric mucosa may be sucked The fragment is then cut off by pulling up the cylindrical knife past the lateral hole by means of a length of wire which traverses the tube to emerge through a vacuum tight gland at the proximal end Suction is applied with a pump through a lateral tube which emerges close to the proximal end The overall length of the biopsy tube is 100 centimetres and levels I II and III are marked 45 55 and 65 cm respectively from the lateral hole in the operating head

Technique The patient is examined fasting and no sedative is given The pharynx is anaesthetised by a gargle with 15 ml of 3 per cent cocaine with adrenalin 1 10 000 A fine stomach tube is passed into the stomach with the patient sitting The stomach is then completely emptied by the patient lying prone on a couch which is inclined to an angle of 30 with the head downmost and by applying suction to the tube with a 20 c c syringe while it is slowly withdrawn Should air or fluid remain in the stomach the chance of obtaining a fragment of mucosa is greatly diminished

The flexible gastric biopsy tube is then passed with the patient lying on his left side the passage through the pharynx being aided by vigorous swallowing Rarely the tip is arrested by spasm at the cardia and this can usually be overcome by encouraging deep breathing and swallowing If still arrested it may pass if the patient sits erect or it may be necessary to administer an inhalation of amyl nitrite

The tube is introduced past mark I till mark II approaches the lips The fragment is then cut off by (*a*) forcing down the blade by means of the control wire to open the lateral hole (*b*) immediately exerting negative pressure by means of the exhaust pump to suck in the fragment (*c*) firmly pulling up the blade

The tube is then withdrawn 2–4 cm and rotated 180 in order to engage a new area of gastric mucosa and the cutting is repeated to obtain a second fragment

* This flexible gastric biopsy tube is manufactured by Drug Houses of Australia Ltd Alfred Place Melbourne Victoria Australia

The tube is removed for inspection and the patient instructed to lie still The fragments of gastric mucosa are located by removing the terminal screw forcing out the cylindrical knife blade and unscrewing the blade The fragments will be found either inside the cylindrical knife blade or more frequently within the steel cylinder which houses the blade They are dislodged from the cylinder by directing a current of air down the tube

The fragments are immediately fixed in 10 per cent formol saline thus providing excellent material for histological examination The instrument is immediately cleaned by flushing it through with a liberal quantity of water and then drying with a stream of air The tube can then be sterilised with Zephiran 1 100 and the knife blade with alcohol The instrument is then placed in a sterile cloth bag It is essential that the knife blade be sharpened after every five operations

After the biopsy has been performed the patient has complete rest lying down for a period of 4 hours Sips of milk are given after 1 hour and a light meal at the end of 4 hours Out patients are then sent home to rest arrangements being made for them to be driven home They return to full work on the following day but within 48 hours they visit the Hospital for a medical inspection to exclude haemorrhage

In our cases gastric biopsy was usually a painless procedure—on rare occasions a minor dull burning sensation was experienced but this was usually caused by vigorously thrusting the tube too far into the stomach thus exerting pressure on the greater curvature for it was immediately relieved by withdrawing the instrument 2–3 cm After the operation was completed a few patients had minor epigastric discomfort for 12–24 hours but the significance of this was difficult to assess as most of them were being investigated for a similar complaint

In general it may be said that gastric biopsy performed with the flexible gastric biopsy tube is not a major undertaking Most patients are quite prepared to have it repeated at intervals of 1 or 2 years

The efficiency of gastric biopsy with the flexible tube The efficiency of this method is shown by the combined experience of a number of operators in our unit Between the years 1948 and 1957 there were 1949 attempts at gastric biopsy with the flexible tube and 89 per cent were successful The unsuccessful attempts were due to failure to obtain a suitable fragment in 6 per cent and the

obtaining of oesophageal mucosa in 5 per cent The 1736 successful biopsies were carried out on 1046 patients many patients having more than one biopsy Thus in one patient 15 successful biopsies were carried out over a period of 8 years

Sampling error As the area of mucosa examined in a single biopsy is so small it is inevitable that a sampling error occurs To minimise and measure this error usually 2 fragments of mucosa are obtained from different portions of the body of the stomach with each passage of the biopsy tube Joske *et al* (1955) found that of 726 cases in 73 8 per cent the appearances in the 2 fragments were similar while in 26 2 per cent there were sufficient differences between the fragments to suggest that the changes were patchy Similarly of 123 patients in whom serial gastric biopsies were carried out 76 4 per cent showed substantial agreement in histology while 23 6 per cent did not Some of the latter were due to known local lesions (ulcer carcinoma) and in others they were related to the changing course of the illness

Studies of operation and autopsy material reveal that gastritis usually involves the body of the stomach fairly diffusely (Hebbel 1949 Williams 1950) Furthermore it has been found that the results of the histamine test meal and the biopsy appearance are related in that the lower the gland content of the section the lower the acidity and output of the gastric juice (Funder and Weiden 1952)

Preparation and staining of biopsy specimens for microscopic examination

The fragment of gastric mucosa obtained by the flexible biopsy tube consists of a disc of tissue approximately 2 mm in diameter and 0 5 mm in depth (fig 3) Immediate fixation is carried out in 10 per cent formol saline for 6 to 12 hours It is then prepared for paraffin embedding in the routine manner

It is essential to obtain vertical sections of mucosa Should difficulty be experienced in achieving this the fixed specimen may be cut perpendicularly to the surface with a sharp scalpel and appropriately placed in the molten paraffin during embedding Sections 5 μ in thickness are cut mounted and stained with eosin and haematoxylin haematoxylin and Mayer s mucicarmine for detecting alterations in the mucus secreting cells and the trichrome stain of Motteram (1951) which is a modification of that

used by Bowie and Vineberg (1935) The trichrome stain is most informative as it clearly identifies the chief and parietal cells It is used as follows

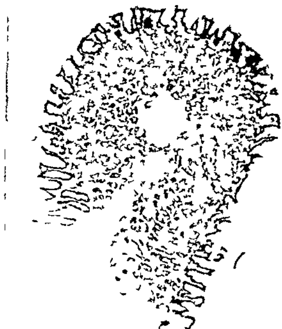


Fig 3 A m il g stric b psy f agment obtained with the flexible gastric biopsy tube to sho the spe imen of mu osa obtained (eosin and h ematoxylin × 45)

Reagents for trichrome stain

1 Pepsinogen stain Stock solution
Methyl violet 6B (1 per cent in aqueous solution)– 100 ml
Orange G (0 5 per cent in aqueous solution)—100 ml
Mix allow to stand overnight centrifuge and wash the precipitate 6 times Dissolve the precipitate in 100 ml absolute ethyl alcohol
For use take 2 parts of the stock solution and add one part of distilled water The stock solution is quite stable in a well stoppered bottle

2 Ponceau—fuchsin—phloxine
Ponceau de xylidine (1 per cent in aqueous solution)—6 ml
Acid fuchsin (1 per cent in aqueous solution)—2 ml

Azophloxine (0 5 per cent in aqueous solution)—2 ml
Acetic acid (1 ml glacial acetic acid in 1500 ml water)—88 ml

3 Methyl green (1 per cent in aqueous solution)

Staining method for trichrome stain

1 Pepsinogen stain—40 minutes in a Coplin jar
2 Decolourise with 70 per cent ethyl alcohol until the violet colour remains in the chief cells only
3 Wash with water
4 Ponceau—fuchsin—phloxine—10 seconds
5 Wash with water
6 Methyl green—60 seconds
7 Differentiate rapidly with 95 per cent ethyl alcohol
8 Dehydrate with absolute alcohol
9 Xylol
10 Mount in Canada balsam

Results of trichrome stain Pepsinogen granules purple parietal cell cytoplasm red Paneth cell granules dark red nuclei bluish green goblet cell mucus green

The appearance of the normal gastric biopsy

Detailed accounts of gastric cytology have been given by Bensley (1928) Plenck (1932) and Maximow and Bloom (1952) Microscopic examination of biopsy fragments from the body of the normal stomach shows the mucosa to consist of a dense aggregation of regular branched tubular glands opening through a neck into the *foveolae gastricae* or gastric pits (fig 4) The epithelium of the pits and glands is supported by a basement membrane formed by a condensation of the *lamina propria* the glands extending down to the *muscularis mucosae* The average depth of the processed section from the surface to the inner aspect of the *muscularis mucosae* is 0 54 mm (Joske *et al* 1955)

The pits extend down into the mucosa for a distance of one third to half of its depth and their lumen (10–40 μ) may be wider than that of the glands The superficial epithelium lining the surface of the mucosa and extending into the pits consists of a single layer of regular tall columnar epithelium with small round or oval basal nuclei and a pale eosinophilic cytoplasm containing a theca of mucigenic granules which stain with mucicarmine Goblet cells are not present in the normal gastric mucosa Smaller mucigenic cells are also present in the necks of the glands Mucus

may be visible in the lumen of the pits forming an adherent layer on the superficial epithelium

Bensley (1928) found mitoses in the cells lining the bases of the pits so that replacement of the rapidly shedding gastric epithelium probably occurs by multiplication of the cells in these areas This is borne out by the progressive differentiation in the cells from the depths of the pits to the surface, sometimes becoming more pronounced during recovery from injury (Motteram 1951) We have not encountered obvious mitoses in the biopsy specimens prepared by our technique but E Palmer (1954) has reported an excellent example in a case of acute alcoholic gastritis

The parietal or acid secreting cells are more numerous in the superficial portion of the glands polyhedral in shape with the deeper cells tending to be displaced laterally from the lumen of the gland Their cytoplasm is eosinophilic The pepsinogen secreting or chief cells are more numerous in the deeper portion of the glands cuboidal or low columnar in shape with basal nuclei and granular cytoplasm Argentaffine cells are not seen in sections stained in the manner described above

In the antrum and pyloric areas the pits are deeper and the glands here consist of coiled tubules lined by low columnar or cuboidal cells with basal nuclei and a pale granular cytoplasm which stains with mucicarmine They resemble the Brunner s glands of the duodenum Interstitial cellularity is more pronounced The glands in the region of the cardia are similar in appearance to the glands of the antrum

The *lamina propria* is a delicate reticulum containing a few fibroblasts plasma cells and lymphocytes Capillaries and lymphatics in this area are occasionally apparent in the sections Occasionally a small lymph follicle is present in the deeper portion of the mucosa In the antrum interstitial cellular infiltration is more pronounced The *muscularis mucosae* forms a lamina at the base of the glands sending an occasional fibre up into the *lamina propria* between the glands In the biopsy the circular and longitudinal fibres are not seen as such because of the random *orientation of the fragment* In some biopsies the connective tissue and small vessels of the submucosa can be seen

Artefacts due to the suction of the biopsy cylinder include small extravasations of red cells under the superficial epithelium and the aspiration of epithelial or gland cells into the lumen of the glands or pits In abnormal specimens both these phenomena are more



Fig 4 *Normal gastric mucosa in a gastric biopsy* With the trichrome stain the parietal (red) and chief cells (purple) are easily distinguished in the glands (Trichrome stain ×80)



Fig 5 *Chronic atrophic ga tritis with moderate atrophy* Patchy intestin l metaplasia with goblet cells in the superficial epithel um The gastric pits are d storted th glands are reduced in number and cont in non spec fic cells The *lamina p opria* is nfiltrated with inflammatory cells (Trichrome stain ×80)



Fig 6 *Gast ic atr phy* The biopsy shows d ffuse int stinal metaplasia and compl te atrophy of the glands (Trichrome stain ×110)

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Fig 4 *Normal gastric mucosa* in a gastric biopsy With the trichrome stain the parietal (red) and chief cells (purple) are easily distinguished in the glands (Trichrome stain ×80)



Fig 5 *Chronic atrophic gastritis with moderate atrophy* Patchy intestinal metaplasia with goblet cells in the superficial epithelium The gastric pits are distorted the glands are reduced in number and contain non specific cells The *lamina propria* is infiltrated with inflammatory cells (Trichrome stain ×80)



F *Gastric atrophy* The biopsy shows diffuse intestinal metaplasia and complete atrophy of the glands (Trichrome stain ×110)

pronounced and may reflect actual changes of this nature or the more ready production of such changes in the abnormal mucosa

The indications for gastric biopsy using the flexible tube

Gastric biopsy is of considerable value in determining the cause of chronic dyspepsia where neither X ray nor gastroscopy reveals an ulcer or cancer Here a biopsy may aid in the diagnosis by showing active chronic gastritis with considerable atrophy of the parietal and chief cells Active chronic gastritis may be the sole cause of the symptoms and signs It must be appreciated however that the biopsy *per se* does not exclude cancer

Biopsy may also indicate gastritis as being the cause of chronic iron deficiency anaemia from continuing blood loss This blood loss is usually in minimal quantity but from time to time there may be a frank melaena and even a haematemesis

Gastric biopsy may also aid in the diagnosis of subacute combined degeneration of the cord where examination of the peripheral blood and bone marrow reveals no clear evidence of pernicious anaemia and where the estimation of serum vitamin B_{12} is not available or is rendered valueless by previous injections of vitamin B_1 The more elaborate absorption tests following the oral administration of ^{56}cobalt labelled vitamin B_1 is also informative in these circumstances (Booth and Mollin 1956 Witts 1956)

Gastric biopsy is contra indicated when there is clinical evidence of a bleeding tendency supported by laboratory tests Also neither gravely ill patients nor patients with severe anaemia should be examined in this way—the latter should first be treated by transfusion or other suitable means to relieve their anaemia This applies to cases of megaloblastic anaemia where the cause is in doubt Should it be true pernicious anaemia the gastric atrophy will remain unchanged in spite of full treatment with vitamin B_1 (Finckh and Wood 1953)

Gastric biopsy will also aid in determining the cause of achlorhydria for there is a close correlation between the gastric biopsy findings and the histamine test meal (fig 1) This was first shown by Wood Doig Weiden and Moore (1949) and more recently by Shiner and Doniach (1957) who found good correlation between gastric biopsy and the secretion of acid and pepsin

Complications of gastric biopsy with the flexible tube

Haemorrhage into the lumen of the stomach was the only complication encountered in our series There was no evidence of gastric perforation—the instrument was designed to cut down to the *muscularis mucosae* and no deeper and this was confirmed by extensive preliminary trials on the bench using fresh specimens of stomach removed at operation Gastroscopy performed immediately after biopsy revealed a minute lesion usually covered by blood clot, at the most there was minimal bleeding There was no evidence of persistent ulceration as judged by the absence of pain X ray examination gastroscopy or examination of the mucosa when subtotal gastrectomy for duodenal ulcer was performed one week or more after the biopsy was taken However a small superficial healing lesion could usually be observed in a stomach resected 1 or 2 days after the biopsy

Using the same model of the flexible gastric biopsy tube and working with cats Gunter (1950) made detailed observations on the rate of healing of the gastric mucosa after biopsy and found that a single layer of regenerating epithelium just covered the lesion in 3 days and experience with humans indicated a similar rate of healing

Haemorrhage sufficient to cause symptoms of anaemia haematemesis or melaena or a pronounced fall in haemoglobin occurred in only 10 of 1947 attempted biopsies 87 per cent of the latter providing suitable fragments of gastric mucosa

Most haemorrhages occurred within 12 hours of the biopsy and caused weakness sweating and pallor followed by the passage of a melaena stool Rarely there was a small haematemesis Limited blood transfusion was required in only 2 of the 10 patients 1 of these was severely and chronically ill with subacute combined degeneration of the cord and bladder sepsis There were no fatalities

In our series haemorrhage has been much less frequent since patients have been kept at strict rest in bed for 4 hours after making the biopsy and since biopsy has not been undertaken in patients showing the bleeding diathesis

Markson and Davidson (1956) encountered 2 cases of haematemesis in 111 gastric biopsies performed with the flexible tube one an elderly male with hypertension and renal insufficiency the other a middle aged female with untreated pernicious anaemia Both responded to blood transfusion Using a modification of the

flexible tube Rubin *et al* (1953) reported haemorrhage in 2 of over 200 biopsies and Coghill and Williams (1955) recorded haematemesis in 9 (2 1 per cent) of 1189 attempted biopsies on 437 patients and also one case of perforation of the oesophagus E Palmer and Smith (1953) reported 2 patients who developed a submucosal haematoma but recovered with conservative treatment

Shiner and Doniach (1957) performed 127 successful biopsies without any complications and there were few failures to obtain a suitable fragment

The best results are obtained by gentle handling of the instrument till it is in position by keeping the head of the instrument stationary while the negative pressure is applied and the knife blade firmly pulled up ensuring that the knife is sharpened frequently and arranging that after the biopsy the patient has absolute rest for 4 hours And finally gravely ill patients and patients with a bleeding tendency should not be subjected to biopsy

Such measures should reduce the complications to less than 1 per cent Severe complications should be rarely encountered

Gastric cytology

Because of our interest in gastric biopsy we have only had limited experience with the study of gastric washings Undoubtedly this method is of value in the detection of gastric cancer and even pernicious anaemia when it is performed by pathologists skilled in this procedure (Massey and Rubin 1954 Crozier *et al* 1956)

CHAPTER 2

ACUTE GASTRITIS

Structural changes

Surely the most dramatic accounts of acute inflammation in the stomach have come from Beaumont (1833) who described the hyperaemia mucus patches erosions and diminution in secretion in the gastric fistula of Alexis St Martin following strong alcoholic beverages and other dietary trauma and during acute febrile episodes These studies have been paralleled in the modern era by Wolf and Wolff (1943) who demonstrated that psychic stimuli in their patient Tom produced acute inflammatory changes in the mucosa of his gastric fistula Gastroscopic appearances in acute gastritis have been recorded by Schindler (1922) and E Palmer (1951) while haematogenous gastritis in fatal infections has been found by Vimtrup (1929) and Nyfeldt and Vimtrup (193-) using the technique of Faber (1935) of early post mortem fixation of the stomach with formalin

The gastric mucosa may be damaged by various chemical bacterial and physical factors nervous stimuli and interference with blood supply The nature of the noxious stimulus its severity duration and portal of entry into the stomach modify the changes occurring in the mucosa Maintenance of the normal gastric epithelial lining is a dynamic process and simple increase in the rate of regeneration of the cells may cope with increased loss of cells due to some damaging agent without actual ulceration but a point is reached when necrosis and desquamation occur too rapidly for immediate regeneration to occur and erosions or more severe ulceration appear

The changes characteristically involve the mucosa diffusely with areas of pronounced hyperaemia rendered patchy by muco purulent exudate mucosal oedema and submucosal petechiae When damage is severe erosions ulceration and even corrosion of the gastric wall may occur

The *microscopic changes* in acute gastritis have been described in

biopsy material by E Palmer (1951) and Motteram (1951) Increased regeneration of cells is reflected by the presence of irregularity of the cell size nuclear size and staining poor cytoplasmic differentiation and arrangement of the superficial epithelial cells These cells may be stratified with indistinct cell borders and containing little or no secretory material in their cytoplasm The changes are often clearly seen occurring in the depths of the pits There is oedema of the superficial *lamina propria* which contains increased numbers of plasma cells and lymphocytes and many polymorphonuclear cells (polymorphs) which penetrate the epithelium Haemorrhages may occur into the interstitium The overall appearance in some cases may resemble chronic superficial gastritis

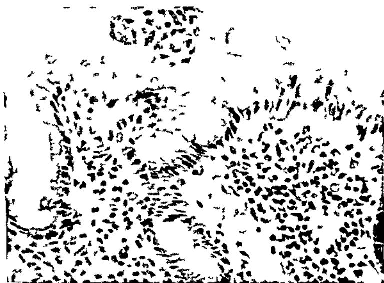


Fig 7 *Act te ga t itis* G stric biopsy from a m le pati nt aged 57 yea s 3 days fter se er alcoholic bout followed by haemat mesis Nec ot c superfi l epithel l c lls a e is ble in the su f ce mu u Th y are regul r in height nd show poor cell outlin In many the mu genic theca is abs nt The *la i n i p p ia i* oedem tou and infiltrated th pla ma c lls lymphocytes and pol morph (o n and h ematoxylin ×600)

More intense stimuli result in frank necrosis of cells which become desquamated into the lumen of the pits and the lining mucus along with migrating inflammatory cells (fig 7) These necrotic foci may desquamate to leave small erosions or even

penetrate the *muscularis mucosae* to become a frank ulcer Williams (1950) considered that erosions were initially produced by the rupture of mucosal capillaries through the superficial epithelium The most severe erosive processes penetrate the gastric wall following necrosis of all coats

When damage to the stomach has been confined to the superficial epithelium of the ridges and pits surface regeneration is probably always complete (E Palmer 1951) However it is unlikely that regeneration of damaged glandular cells can occur to the same extent and these cells may permanently disappear or be replaced by non specific or mucus secreting epithelium termed pseudopyloric glands Damage to the submucosa muscle and serous coats may be followed by the formation of granulation tissue and even deformity of the organ particularly in the antral region

Symptomatology

Acute gastritis of minor severity is frequently encountered in clinical medicine the symptoms lasting from a few hours to 2 or 3 days Anorexia nausea occasional vomiting and diffuse epigastric discomfort and tenderness are the outstanding features

In a severe case the onset is usually sudden with pronounced epigastric pain persistent nausea and vomiting perhaps with traces of blood on occasions there may be a profuse haematemesis The patient is weak thirsty drowsy and soon shows the effects of toxaemia dehydration and electrolyte depletion He is pale with sunken eyes inelastic skin rapid pulse low blood pressure muscular cramps and excessive thirst The urine is scanty deficient in chlorides and may contain a trace of albumen The temperature may be subnormal at first and later elevated There may be constipation or diarrhoea The abdomen is usually sunken but later may become distended The tenderness is diffuse with maximum intensity in the epigastrium The nature and duration of the symptoms are largely determined by the cause of the acute gastritis Thus in acute staphylococcal food poisoning due to the ingestion of staphylococcal enterotoxin the gastric symptoms predominate whereas in acute staphylococcal gastroenteritis and in *Salmonella* infections the intestinal symptoms predominate with diarrhoea and generalised abdominal tenderness

E Palmer (1951) made a valuable study of the stomach in

acute exogenous (staphylococcic) gastroenteritis due to ingestion of food heavily contaminated by staphylococci and their toxins He investigated 42 previously healthy male subjects aged between 17 and 47 years 38 of whom had been involved in 1 of 3 major outbreaks of 'food poisoning On most of them a gastric biopsy was performed with a modified flexible gastric biopsy tube and followed with gastroscopy The subjects were examined in this way at intervals varying between 5 and 580 hours after the onset of the symptoms These symptoms usually consisted of vomiting retching chills fever and perhaps some circulatory collapse Six patients were examined in the acute stage 5-12 hours after the onset and all showed abnormal gastroscopic appearances the majority having hyperaemia oedema erosions petechiae and purulent exudate The same 6 patients were subjected to gastric biopsy during the acute stage and 5 showed pronounced histological changes the remaining patient was examined 5 hours after the onset of symptoms and showed no histological change but at gastroscopy there was congestion of the mucosa

The essential histological lesion in these 5 early biopsies was congestion and oedema followed by necrosis of cells at the junction of the pits and glands the damaged cells then being extruded to the surface with exfoliation and erosion Regeneration of the epithelium was accompanied by interstitial inflammatory cell infiltration

Twenty four patients were subjected to gastric biopsy and an abnormal gastric mucosa was present in 5 of 6 examined in the first 12 hours all of 4 examined between 26-40 hours 4 of 7 examined between 50-82 hours and 0 of 7 examined between 92-220 hours

These splendid studies of E Palmer would therefore suggest that in relatively young individuals a single severe attack of acute gastritis causes considerable inflammatory changes in the gastric mucosa and this is followed by complete healing It may be that if the attacks were frequent if the subjects were older or if greater numbers had been studied then evidence of the persisting changes of chronic gastritis would be forthcoming No studies of gastric secretion were reported in E Palmer s series but it is anticipated that there would have been a depression of acid and pepsin secretion during the acute phase with a return to normal levels with the subsidence of the inflammatory changes

E Palmer (1954) has also studied the acute gastric symptoms and the gastroscopic and biopsy findings in cases of acute alcoholism (see Chapter 3) He concluded that following an acute alcoholic bout there was evidence of acute gastritis, but that usually there was complete resolution

However it is our experience that if the alcoholic bouts are severe and often repeated then persistent change may be established the mucosa changing from acute superficial gastritis to chronic atrophic gastritis and perhaps after the course of many years even to gastric atrophy The factor of chronic malnutrition also plays a part (Joske and Turner 1952) (*vide infra*)

Aetiology

A number of chemical dietary bacterial as well as psychic stresses may produce acute gastritis The corrosive action of agents such as caustic soda phenol and mineral acids gives rise to an acute corrosive gastritis in which the stomach wall may perforate Should the patient survive healing with fibrosis and distortion of the stomach occurs

In Australia the commonest dietary irritants implicated in acute gastritis are the strong alcoholic beverages Motteram (1951) illustrated the histological features of the gastric mucosa of a patient from whom a gastric biopsy was obtained 3 days after a haematemesis brought on by a severe bout of alcoholism Necrotic surface epithelium was present with replacement by actively proliferating epithelial cells growing out from the pits while red cell extravasations were visible in the *lamina propria* (fig 7)

Finckh *et al* (1952) examined the gastric biopsies of 39 chronic alcoholics Abnormal gastric mucosa was found in 18 Of these superficial gastritis was present in 14 and atrophic gastritis in 4 Of the cases with superficial gastritis 5 showed subsequent resolution suggesting that the lesion had been acute and reversible

Later similar figures were obtained in our unit by Joske *et al* (1955) who found 51 out of 95 gastric biopsies obtained from alcoholic subjects showed evidence of gastritis Williams (1956) found similar changes in a group of 25 alcoholics submitted to gastric biopsy He also carried out animal experiments which suggested that alcohol consumed in the concentrations found in fortified wines and spirits may cause haemorrhage erosions and ulceration especially if taken on an empty stomach

Nyfeldt and Vimtrup (1932) examined the stomach of children dying of diphtheria and found evidence of acute gastritis This was considered to be due to circulating diphtheria toxin for when the stomachs were fixed soon after death and subsequently examined there was no evidence of diphtheritic bacterial invasion Thomsen (1925) produced gastritis in dogs by the injection of diphtheria toxin Vimtrup (1929) also found acute gastritis at the post mortem examinations of patients dying from influenza and pneumonia

As previously stated E Palmer (1951) performed gastroscopy and gastric biopsy on 42 patients with acute staphylococcal food poisoning and observed the gastritis beginning some hours after the onset of symptoms and usually disappearing within 2 to 4 days without residual damage to the mucosa

Treatment

The treatment of acute gastritis depends on the cause and severity of the attack In the commonest form which is associated with mild food poisoning rest free fluids and probably a saline purge is all that is required

The severe attacks may be associated with a specific bowel infection and the causal organism should be sought by culture of a fresh specimen of stool Transfer to hospital is essential Antibiotics and sedatives together with the intravenous infusion of electrolytes glucose and perhaps blood or serum may be indicated As the patient improves increasing oral feeding is given

CHAPTER 3

CHRONIC GASTRITIS

Structural changes

Reports of chronic inflammatory changes in the gastric mucosa were criticised and discredited for many years on the grounds that they were caused by post mortem autodigestion Satisfactory post mortem material was first obtained by Faber and Bloch (1900) using intraperitoneal injection of formalin immediately after death The pathology of chronic gastritis has since been amply demonstrated by Faber (1935)

The results of the examination of specimens of stomach obtained at operation were recorded by Konjetzny (1928) but have been criticised by Schindler (1947) Schindler *et al* (1939) and Sanders and Mecray (1941) showed that acute erosions of the mucosa could develop during the actual resection of the specimen Schindler and Ortmayer (1942) obtained stomach biopsies through an abdominal incision but of course this procedure is unsuitable for routine use

Chronic inflammatory lesions were described in biopsy frag ments obtained through oesophageal tubes by Swalm *et al* (1936) while Kenamore *et al* (1946) Benedict (1948) and d Almeida (1948) recorded similar findings in mucosal biopsies The use of a flexible gastric biopsy tube (Wood *et al* 1949A) has enabled serial biopsies to be made on patients with chronic gastritis im mediate fixation of the fragments ensuring freedom from autolysis

In chronic gastritis there is a wide variety and a continuous spectrum of structural changes Attempts to classify these changes into different types tend to overlook the variations of distribution severity and activity which may occur in the same patient over a period of time A relationship to the clinical features of gastritis is best achieved by classifying according to alterations in the thickness of the mucosa the concentration of chief and parietal cells and the extent and activity of the inflammatory processes Thus three main types of gastritis can be recognised

1 *Superficial gastritis* Here there is superficial inflammation of the mucosa without atrophy of the glands The mucosa is of normal width and while the inflammatory changes may be slight moderate or severe the lesion is capable of complete resolution However the changes may persist as a chronic superficial gastritis or with recurrences may progress to atrophic gastritis

2 *Atrophic gastritis* There is a more diffuse inflammation of the mucosa showing varying degrees of activity coupled with slight moderate or severe atrophy of the specific parietal and chief cells usually leading to a decrease in the width of the mucosa While the inflammatory changes may resolve to some degree there are permanent changes in the epithelial structures and only partial regeneration of the parietal and chief cells occurs Recurrent exacerbations of inflammation lead to a severe atrophy which may closely resemble primary gastric atrophy (see Chapter 5)

3 *Gastric atrophy* This is the classical change seen in pernicious anaemia and subacute combined degeneration of the cord It is included here for the sake of completeness as this change may result from the subsidence of the inflammatory changes in a severe case of atrophic gastritis or alternatively it may be due to a primary atrophy of the mucosa This is discussed later together with the histological picture (see Chapter 5)

Diffuse giant hypertrophic gastritis This is a further rare variety which is described in Chapter 4 It probably represents a different disease to chronic gastritis

Macroscopic appearance in chronic gastritis There may be little alteration from normal appearance In severe cases the mucosal surface may appear granular or mammillated the mucosa thin and the rugae small (fig 8) The granularity may be the result of oedema cellular infiltration lymphoid infiltration or cystic change in the epithelial structures However the degree of distension of the stomach must always be considered when estimating mucosal thickness and the size of rugae—lack of appreciation of this has led surgeons gastroscopists and radiologists to make an erroneous diagnosis of hypertrophic gastritis (fig 9)

Hebbel (1949) found wide variation in the distribution of chronic gastritis Local changes were common in the antrum and along the lesser curvature and the presence of changes in these sites was not necessarily indicative of more diffuse changes in the mucosa However he claimed that changes along the greater curvature

Fig 8 *Chronic atrophic gastritis* Stomach obtained *post mortem* from a male patient aged 64 years with severe chronic atrophic gastritis previously proven by gastric biopsy The mucosa is smooth finely granular or slightly nodular The rugae are flattened and have largely disappeared an appearance which may have been caused by terminal gastric dilatation (natural size)

Fig 9 *Normal gastric mucosa* in contracted stomach fixed soon after death The rugae are full and regular With distension of the stomach they become less prominent (natural size)

occurred usually as part of a more diffuse process in the body of the stomach

Microscopic appearances in chronic gastritis The changes in the gastric biopsy may range from slight superficial increase in plasma cell infiltration of the *lamina propria* to gross alteration in the epithelial structure disappearance of the specific glands and infiltration and replacement by mesenchymal elements These appearances are best considered under the headings of superficial gastritis and atrophic gastritis although there is no clear dividing line between the two

Superficial gastritis The most constant feature is the presence of inflammatory cells in the superficial regions of the *lamina propria* Where there is only a slight increase of plasma cells unaccompanied by superficial epithelial changes this may be considered to be within physiological limits The pathological range is considered to be reached when there is more pronounced plasma cell infiltration polymorphonuclear cells are seen migrating singly or in groups from the *lamina propria* to penetrate the superficial epithelium and lie in the pits or superficial mucus (fig 10) Some red cells may be extravasated into the superficial *lamina propria* and there is lymphocytic infiltration of the deeper layer (fig 11)

In acute exacerbations of the gastritis superficial epithelial cell damage is sometimes evident as groups of poorly staining cells in the adherent mucus (fig 7) but a more common feature is the evidence of cell regeneration in the form of irregular or smaller flattened cells Sometimes these epithelial cells are stratified and show indistinct cell borders poor differentiation and little or no secretory material in their cytoplasm the nuclei vary in size often being large and hyperchromatic

These changes are sometimes most pronounced in the pits where there is dilatation or cystic change lengthening tortuosity and distortion due to extension of the regenerating cells down into the glands as well as up to the surface Sometimes this is due to obstruction of the lumen of the pit The basal two thirds of the mucosa are normal and the total width of the mucosa is unchanged Should it be possible to remove the damaging agent the mucosa may return to a normal appearance in 2 to 3 weeks

The histological appearance of chronic superficial gastritis may be identical with that of acute gastritis Chronicity of the lesion

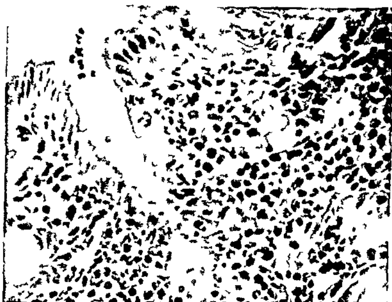


Fig 10 *Active superficial gastritis* showing intensive polymorphonuclear infiltration of the *lamina propria* with penetration of the superficial epithelium by the polymorphs (eosin and haematoxylin × 400)



Fig 11 *Gastric biopsy showing superficial gastritis* The superficial epithelium is flattened and irregular There is infiltration of the superficial *lamina propria* by plasma cells and polymorphs There are some lymphocytes deeper in the *lamina propria* (eosin and haematoxylin × 150)

is only established by the duration of the symptoms or more convincingly by repeated biopsy when persistent superficial gastritis or perhaps progression to atrophic gastritis is seen

Atrophic gastritis In atrophic gastritis the changes in the superficial portion of the mucosa are identical with those in superficial gastritis but the inflammatory changes now extend to involve the lower two thirds of the mucosa with slight (fig 12) moderate (fig 5) or severe atrophy of the glands (figs 13 14 15) The average depth of the mucosa in the processed section varies from 0 47 mm in gastritis with slight atrophy to 0 45 mm in those with severe atrophy (Joske *et al* 1955)

Groups of plasma cells and polymorphs are seen in the superficial *lamina propria* while lymphocytes are more prevalent in the deeper areas where they may be aggregated into follicles near the base of the mucosa Occasionally fat cells develop close to these follicles (fig 16) The intervening areas of *lamina propria* contain a delicate connective tissue network which may be oedematous but dense collagenous fibrosis does not occur Sometimes these mesenchymal elements replace the glands completely and often separate the fibres of the *muscularis mucosae* which becomes thickened (fig 17)

The irregularities of the superficial epithelium extend into the glands and the chief and parietal cells are partially or wholly replaced by mucus secreting or non specific cells arranged in coiled pseudopyloric glands a form of post inflammatory metaplasia of the epithelium (fig 18)

Another form of metaplasia is to an intestinal type of gland (Magnus 1937) which is characterised by the appearance of a superficial epithelium containing tall columnar cells with a darkly staining surface interspaced with goblet cells (fig 18) They are arranged to form a crypt with argentaffin cells and at the base Paneth cells The Paneth cells contain coarse eosinophilic refractile granules which stain a dark red with the trichrome stain (fig 19) By means of silver stains argentaffin cells can be demonstrated lying laterally in these crypts (fig 20) (Magnus 1937) This metaplasia is patchy in character more confined to the pits and usually seen to occur abruptly in a single high power field (fig 21)

In spite of these atrophic changes in the glands the mucosa may not be decreased in depth owing to infiltration with inflammatory cells and oedema

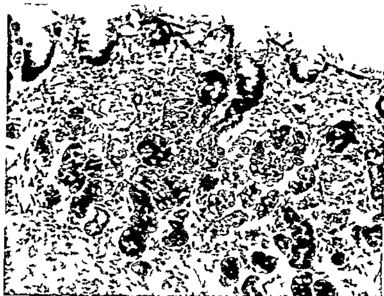


Fig 12 *Gastric biopsy showing chronic gastritis with slight atrophy of the glands* (trichrome stain × 150)



Fig 13 *Chronic atrophic gastritis with severe atrophy* A female aged 64 years with recurrent abdominal pain anaemia and achlorhydria for 22 years following *an* episode of gross malnutrition Gastric biopsy showing severe inflammatory infiltration of the *lamina propria* with polymorphs plasma cells and lymphocytes A lymph follicle has formed at the right The specific glands have almost completely disappeared During the ensuing 8 years serial biopsies and test meals remained unchanged (eosin and haematoxylin × 150)



Fig 14 *Chronic at ophic gast itis* Castric b opsy from same case as fig 13 The biopsy shows distortion and elongation of the pits disappearance of most of the glandul r tubules and a severe inflammatory infiltration of the *la ina propr a* (trichrome stain × 150)



F g 15 *Cl ronic atropl gast tis* showi g cystic change in the pits ith ps udopyloric metaplasia of the glands (eosin and haematoxylin × 150)



Fig. 16 *Chronic atrophic gastritis* Lymphoid tissue and fat are replacing the specific glands (eosin and haematoxylin × 180)



Fig 17 *Ch onic gast itis* There is splintering and th cken ng of the *musci l is mucosae* by inflammatory cells (eosin and haematoxylin × 180)

With gross atrophy of the glands and post inflammatory metaplasia the end result resembles primary gastric atrophy Differentiation between atrophic gastritis and gastric atrophy is made on the histological characteristics (Table 3 Chapter 5)

Symptomatology of chronic atrophic gastritis

The symptoms of chronic atrophic gastritis are distinctive and show but little variation from patient to patient The patient is usually a female over 40 years of age Doig and Wood (1952) found a female male ratio of 5 4 and this female predominance was increased when the alcoholics were excluded The patient s discomfort varies from a sense of excessive fullness in the epigastrium especially after taking food to a dull burning pain The site of her distress is diffusely situated in the epigastrium In contrast to peptic ulcer where the patient usually demonstrates the site of the pain and tenderness by pressing in deeply with the tips of the fingers she rubs the epigastrium from side to side with the flat of her hand saying This is where I have the discomfort (or the pain) across here Rarely pain may also be felt in the back and thus may mimic a penetrating ulcer chronic pancreatitis or cancer Like gastric ulcer the pain of gastritis most frequently occurs immediately after taking food or within half an hour

It is paradoxical that although most of the patients have hypochlorhydria or achlorhydria their discomfort is relieved by taking alkaline powder Hydrochloric acid taken with their meals may produce relief but in our experience most patients claim they receive no benefit or are made worse—they usually prefer alkaline powder

Certain foods may aggravate the pain particularly fat pineapple cabbage and condiments although there is great variation from patient to patient There are exacerbations and remissions in the symptoms the exacerbations being brought on by an associated illness undue mental or physical stress or over indulgence in alcohol Lack of appetite is common and may lead to loss of strength and weight this in turn may create a fear of cancer in the mind of the patient and indeed in the mind of the physician Adding to this fear may be the finding of hypochromic anaemia and occult blood in the stools resulting from gastric erosions

Occasionally especially in alcoholic gastritis haematemesis or melaena is encountered and thus gastritis must be considered a



Fig 18 *Types of mucus secreting cell in chronic gastritis* from same biopsy as fig 5 On the upper left hand side the normal mucigenic theca of the superficial gastric epithelium is visible On the upper right hand side the goblet cells in areas of intestinal metaplasia stain heavily In the base of the mucosa pseudopyloric mucus secreting cells are increased in amount replacing parietal and chief cells (mucicarmine × 150)



Fig 19 *Chronic atrophic gastritis Intestinal metaplasia* A crypt containing dark intestinal type tall columnar epithelium and some goblet cells Dark granules are visible in the Paneth cells (trichrome stain × 600)



Fig 20 *Chron c at pl ic gastr ti Intestinal n etapla ia* Argentaffin cells are visible at the base of the columnar cells wedged in between them (Masson s silver impregnation × 600)

Fig 21 *Cl on atroph gast itis Intest nal metapla ia* Gastric b opsy with a focus of int stinal metaplasia in th superfic al ep thel um There is an abrupt chang from the normal regular tall columnar gastr c epithelium on the right hand s d to the deeper sta n ng columna cells w th the dark border and gobl t lls on the left hand sid (os n and haematoxylin × 600)



Fig 18 *Types of mucus secretin cell in chronic gastritis* from same biopsy as fig 5 On the upper left hand side the normal mucigenic theca of the superficial gastric epithelium is vi ible On the upper right hand side the goblet cells in areas of intestinal metaplasia stain heavily In the base of the mucosa pseudopyloric mucus secreting cells are increased in amount replac ng parietal and chief cells (mucicarmine × 150)



Fig 19 *Chronic atropl ic gastritis Intesti al m tapl isia* A crypt contain ng dark intestinal type tall columnar epithelium and some goblet cell Dark granules are visible in the Faneth cells (tri hrome st n × 600)

aged She is intelligent but may wear a worried expression There may be cracks at the angle of the mouth and atrophy of the tongue The finger nails are brittle with longitudinal furrows rarely koilonychia There is diffuse epigastric tenderness but no mass or rigidity The liver and spleen are not palpable except when pronounced malnutrition is present usually due to chronic alcoholism Examination of the nervous system reveals no abnor mality except perhaps some diminution of the knee and ankle jerks

Although the above description does represent a proportion of cases many reveal no abnormal findings on physical examination except perhaps slight epigastric tenderness during an exacerbation in the disease

Aetiology of chronic atrophic gastritis

Chronic atrophic gastritis is a more advanced stage than super ficial gastritis and results from some damaging processes either intermittent or continuous the nature of which is often obscure Once the gastric mucosa has reached the chronic atrophic stage usually there are few signs of recovery of the mucosa as revealed by improvement in the test meal or the gastric biopsy

Factors which may play a part in the production of chronic atrophic gastritis are sex advancing age perhaps due to increas ing atherosclerosis with depleted blood supply of the gastric mucosa chronic debilitating diseases chronic alcoholism asso- ciated with malnutrition and the drinking of other gastric irritants prolonged psychic stress and finally irradiation of the stomach especially X ray irradiation either in the treatment of abdominal malignancy or in the purposeful production of achlorhydria in the treatment of duodenal ulcer

It is of interest to consider some of these factors in greater detail

TABLE I *Sex distribution in chronic gastritis diagnosed by gastric biopsy*

There was a preponderance of females especially amongst the cases of superficial gastritis (Doig and Wood 1952)

	Males	Females	% Females
Superficial gastritis	12	36	75
Atrophic gastritis	28	36	56
Total	40	72	64

cause of overt upper gastrointestinal bleeding However it is most unusual for the bleeding to be of sufficient severity to warrant a laparotomy Severe and persistent bleeding favours the diagnosis of a peptic ulcer cancer or bleeding oesophageal varices

The bowels function normally or there may be intermittent constipation Although hypochlorhydria or achlorhydria is the rule, attacks of diarrhoea are rare

The age of onset of the pain is of interest Doig and Wood (1952) found that whereas the pain of duodenal ulcer usually began in the mid thirties the pain of gastric ulcer superficial gastritis and atrophic gastritis usually began in the mid forties When the age of first examination in hospital was studied it was found that patients with superficial gastritis were younger than those with atrophic gastritis Doig and Wood concluded that gastric ulcer is more closely related to gastritis than to duodenal ulcer and that atrophic gastritis is a more advanced stage of superficial gastritis

In a survey of 623 patients in the Royal Melbourne Hospital mostly gathered from our unit which was primarily interested in gastroenterology Joske Finckh and Wood (1955) found 221 cases with pronounced atrophic gastritis In 40 per cent of these there were gastro intestinal symptoms considered to be entirely or in part due to the gastritis whereas 23 per cent had gastro intestinal symptoms due to other causes and 37 per cent had no gastro intestinal symptoms

In 50 patients the symptoms were considered to be entirely due to the gastritis It is our firm belief based on extensive experience with proven cases of chronic atrophic gastritis that these subjects may suffer pain and flatulence due to the inflammatory reaction in the gastric mucosa and to deny this cause of dyspepsia is a grave error of medical judgement It is obvious from the above survey that chronic atrophic gastritis may be present without symptoms but of course this in no way invalidates the belief that pain may occur in other subjects and that occasionally it may be moderately severe It should be recalled that gall stones chronic pancreatitis and even pronounced peptic ulceration may be present without symptoms and it could never be claimed that these diseases rarely or never produce discomfort or pain

Physical examination Although chronic atrophic gastritis occurs in both sexes and even in the third decade it is typically seen in an elderly female with grey hair and perhaps prematurely

gastritis These may be explained partly on the basis of malnutrition partly by *circulating toxins damaging the mucosa* In Sjogrens disease where there is atrophy of the lacrymal and salivary glands with depleted secretion and recurring inflammation in the eyes and mouth gastric biopsy may reveal gastritis with varying degrees of atrophy (fig 22) (Joske *et al* 1955)

It is of interest that in haemochromatosis there is deposition of iron in the deeper layers of the gland cells (Althausen Doig *et al* 1951) but as a rule there are few degenerative changes (fig 23) In 15 gastric biopsies Joske *et al* (1955) found iron deposits in all yet 9 were otherwise within normal limits and 6 showed only superficial gastritis This is in contrast to the changes in the liver *and pancreas in this disease*

Chronic gastritis due to chronic alcoholism and malnutrition Chronic alcoholism is quite frequently associated with varying degrees of gastritis although some individuals can tolerate excessive intake of alcohol without developing persistent changes It is probable that after an alcoholic bout the mucosa shows the signs of acute gastritis but it heals without residual change Thus E Palmer (1954) selected 34 young men who were physically fit and not alcoholics and examined them by gastroscopy and gastric biopsy *within 6 hours of an alcoholic bout* Thirty showed acute exogenous gastritis to gastroscopy and all 34 had abnormal biopsy findings mostly superficial gastritis and resembling the acute changes seen in acute staphylococcal food poisoning (E Palmer 1951) Eleven of the 34 were submitted to a second biopsy after an interval of 7–20 days during which time they took no alcohol Nine of the biopsies were now within normal limits

Palmer (1954) also studied the history of alcoholism amongst 200 patients *selected at random whose gastric biopsy was then* within normal limits and found that during the previous 12 months 112 admitted being drunk at least once 81 at least 12 times and 18 at least once a week Palmer wisely accepted their statements with caution However it would seem that excess consumption of alcohol does not always cause chronic gastritis This of course does not indicate that it may not do so in certain susceptible individuals *especially when malnutrition is a pronounced feature* Palmer does not relate whether there were other features of chronic alcoholism in these subjects such as disease of the brain peripheral nerves or liver However he concludes by favouring

Sex Sex appears to play a role in the aetiology of gastritis for females are more commonly affected than males even though alcoholism favours the male incidence 71 per cent of the alcoholics in our unit being males Doig and Wood (1952) reported that amongst cases of superficial and atrophic gastritis 64 per cent were females (Table 1) This increased incidence amongst females suggests an endocrine factor or perhaps malnutrition as Australian housewives are prone to favour a diet high in carbohydrate and deficient in protein and vitamins (Epstein *et al* 1950) However Fairley Joske and Turner (1955) could not find convincing evidence that malnutrition played a leading role

Ageing and the gastric mucosa The age of onset of the symptoms of gastritis varies greatly the average being 44 years (Doig and Wood 1952) Our experience indicates that atrophic gastritis results from a progression from superficial gastritis and that once the stage of atrophic gastritis is reached the condition rarely reverses with healing It is therefore to be expected that gastritis becomes more frequent with advancing age That it is by no means invariably present in elderly subjects has been revealed by E Palmer (1954) who carried out gastric biopsy in subjects over the age of 60 who were not suffering any dyspepsia and found 30 with normal gastric mucosa

Moreover Joske and his colleagues (1955) performed gastric biopsy on 214 patients over the age of 60 and found 18 per cent had normal gastric mucosa Many of the patients in this series were examined because chronic gastritis was suspected so there was a bias towards an abnormal gastric biopsy finding It is of interest that in the same series 218 subjects aged between 20 and 40 years were examined by gastric biopsy and 105 (47 per cent) had normal gastric mucosa Although most of the subjects in this group were suffering from dyspepsia the group included cases of duodenal ulcer where the biopsy is usually normal and also normal subjects without dyspepsia who acted as controls so there was less bias towards an abnormal mucosa

When achlorhydria is found in an elderly individual it is probably due to chronic gastritis and it should not be considered to be a normal finding any more than chronic nephritis or chronic bronchitis is considered to be normal in the aged

Chronic debilitating diseases Diseases such as chronic infections ulcerative colitis rheumatoid arthritis chronic nephritis and long standing malignancy may be associated with chronic atrophic

the idea that although acute alcoholism may cause acute gastritis chronic gastritis rarely if ever is a direct result of chronic alcoholism We disagree most emphatically with his opinion

Indeed Doig and Wood (1952A) surveyed 112 cases of gastritis and found 19 were chronic alcoholics This series was later extended by Joske Finckh and Wood (1955) who reported that of 95 biopsies on alcoholic subjects 39 showed superficial gastritis 11 atrophic gastritis and 1 gastric atrophy without overt pernicious anaemia Our experience with serial biopsies over many months indicates that whereas superficial gastritis amongst alcoholics may resolve should the patient quit his alcoholic indulgences a rare happening it more often progresses to severe atrophic gastritis with continuing alcoholic bouts Moreover the severe atrophic gastritis suffered by a chronic alcoholic rarely resolves with regeneration of the chief and parietal secreting cells even though the intake of alcohol be reduced or even withheld for a year or more—the chronic gastritis has passed the point of no return

Whether alcohol acts directly on the gastric mucosa either by bathing and irritating its surface or by way of the blood stream is a matter of debate and it may well be that it acts by both these means Moreover chronic alcoholism is frequently associated with chronic malnutrition deficiencies in protein and vitamins of the B group being most commonly encountered These deficiencies probably play a part in the atrophic changes in the gastric mucosa just as may be clearly seen in the tongue

In this regard it is of interest to note that Fairley *et al* (1955) carried out a dietetic survey on 30 cases of chronic atrophic gastritis followed for a period of 5 years or more Although they could not determine a clear relationship between chronic atrophic gastritis and malnutrition they found that 5 patients had taken a consistently poor diet and 9 a poor diet for several months It is anticipated that studies on a greater number of cases will provide further evidence that malnutrition may lead to atrophic gastritis and that even though a suitable diet with added vitamins is instituted the change in the gastric mucosa may be irreversible

Hot tea and gastritis Edwards and Edwards (1956) have studied tea drinking amongst 155 subjects with dyspepsia in whom gastric biopsy had recently been performed and they produced evidence that the drinking of excessively hot tea favoured the development of gastritis On the other hand it may be that the sufferer from chronic gastritis is soothed by hot beverages so that chronic



Fig 22 *ltropl ic gastritis in Sj grens disease* Gastric biopsy from female patient aged 60 years ith classical Sjogren s disease including conjunctivitis dry mouth arthritis and achlorhydria There is intense inflammatory infiltra tion of the *lami a propria* disappearance of glands and some foci of intestinal metaplasia in the elongated pits (trichrome stain × 150)



Fig 23 *Haemocl romatosis* Gastric biopsy from a female p tient g d f o y s with pigmentation hepatomegaly and deb lity I i er b opsy sho d i rhosis and gross accumulat on of iron The glandular epithel um f th stoma h contains iron granules (prussian blue stain × 600)

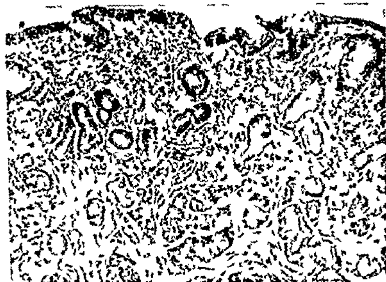


Fig 24 *Radiation gastritis* A male patient aged 34 years with a chronic duodenal ulcer was given deep X ray therapy to the stomach A gastric biopsy taken 66 days after therapy shows active gastritis with atrophy The superficial epithelium is flattened and irregular and shows polymorphonuclear penetration The pits are elongated and distorted and the glands contain many non specific or mucus secreting cells There is a heavy infiltration of the *lamina propria* by polymorphs plasma cells and lymphocytes At this stage histamine test meal showed achlorhydria During the next 2 years serial biopsies and histamine test meal revealed a return to normal (see fig 25) (eosin and haematoxylin × 150)



Fig 25 *Radiation gastritis* (a [illegible] biopsy from same patient as fig 24 taken 2 years after irradiation of the stomach when the histamine test meal had returned to normal level) The mucosa is almost within normal limits (eosin and haematoxylin × 150)

gastritis favours the drinking of hot tea rather than the contrary There is no evidence that tea *per se* is a direct cause of gastritis

Psychic stress It has been shown by Wolf and his colleagues (1948) that psychic stress may cause congestion of the gastric mucosa and also the colonic mucosa and that if the stimulus is severe and prolonged erosions and bleeding may occur Moreover Gray *et al* (1953) found that stress increased the peptic activity of gastric juice It is possible therefore that long continued stress may lead to chronic atrophic gastritis Psychic stress certainly aggravates the symptoms in an established case of gastritis

Gastritis due to X ray irradiation The use of X ray irradiation to reduce the secretion of acid and pepsin in the treatment of duodenal ulcer was first advocated by Bassler in the United States of America in 1909 and later was reported by Holman and Lewis (1941) in Tasmania and Ricketts and his colleagues (1948) in Chicago In 1957 the Chicago group (Levin *et al* 1957) published a follow up of 723 patients and claimed an improvement in the relapse rate compared with the control series However there were 6 deaths from cancer in the test series 2–13 years after the irradiation (*vide infra*) *In 1948 these workers studied the changes* in the gastric mucosa in their duodenal ulcer series following X ray irradiation by taking sections at operation or *post mortem*

In 1951 serial biopsies with the flexible tube were carried out in similar cases in our unit and the morphological changes following X ray irradiation were correlated with the secretion of acid and pepsin (Doig Funder and Weiden 1951) One patient with *chronic duodenal ulcer had biopsies taken 21 38 66 136 374* and 465 days following a gastric tissue dose of 1500 r given over a period of 3 weeks (figs 24 and 25) The morphological picture of the gastric mucosa changed from normal to one of atrophic gastritis of moderate severity with corresponding depletion of the acid and pepsin secretion the maximum changes being observed during the first 3 months There was then a slow return towards normal of the histological changes and secretion with almost complete restoration to normal at the end of a year However the secretions returned to normal levels rather than the high levels which preceded treatment

This case is representative of the majority treated by us and is in keeping with the findings of the Chicago group However there is a considerable individual variation some patients proving very susceptible and later showing little or no mucosal regeneration or

when she was working in the X ray department for a period of 8 months During this time she frequently assisted in prolonged screening examinations to test diaphragmatic movement in severely paralysed patients There was histamine fast achlorhydria and gastric biopsy revealed severe atrophic gastritis Her duties were changed and her symptoms gradually improved over the next 3 years but the achlorhydria and atrophic gastritis persisted

We have had no experience with the radiation hazards other than X rays but it may be that with the coming of the atomic age radiation will play an increasing part as a cause of gastritis

Relationship of chronic gastritis to peptic ulcer

Doig and Wood (1952) studied the relationship between the age of onset of gastric ulcer superficial gastritis and atrophic gastritis and found the average age to be similar being 44 43 and 46 years respectively whereas the average age of onset of duodenal ulcer was significantly less being 36 years It may be that gastritis in its superficial and atrophic forms may be related to gastric ulcer but not to duodenal ulcer which may have a different aetiology If gastritis in its initial stages is patchy and limited in extent it may lead to some superficial ulceration The remaining normal mucosa may then secrete sufficiently concentrated gastric juice to cause further breakdown of tissue with extension of the ulcer in size and depth However should the gastritis in the first place be widespread it reduces acid and pepsin secretion and thus minimises the tendency to chronic ulceration

A gastric ulcer with its zonal gastritis (fig 27) forms an area of impaired gastric secretion and thus tends to limit gastric secretion Thus in gastric ulcer there is reduced secretion of acid and pepsin compared with duodenal ulcer where the mucosa of the body of the stomach is normal or near normal (Perry *et al* 1956)

In an investigation of 98 cases of duodenal ulcer Doig and Wood (1952C) found 60 per cent with normal gastric mucosa and 30 per cent with superficial gastritis without atrophy Cox (1952) studied the secreting bulk of gastric mucosa in patients with duodenal ulcer and found it to be in excess of normal This has not been apparent in our biopsy studies Magnus (195-) found the mucosa of the body of the stomach to be normal in most cases of duodenal ulcer but that a slight to moderate degree of antral gastritis might occur

return of secretions others showing only a minor reaction with rapid return to normal of both structure and secretions With increasing dosage of X rays the changes became more pronounced and more prolonged (Levin *et al* 1957 Brown and Wood 1955)

It is of interest that most patients subjected to radiation gastritis suffer little or no discomfort *true pain rarely being reported* It may be that the pain nerve endings in the stomach wall have been rendered insensitive by the X ray irradiation

Other studies were made in our unit of cases of duodenal ulcer treated by antroduodenectomy followed by X ray irradiation In antroduodenectomy the antrum and most of the first part of the duodenum including the ulcer were removed followed by end to end anastomosis the irradiation served to reduce the high acid secretion which persisted after the operation (Brown *et al* 1952 Brown and Wood 1955 and 1956) Fig 26 shows that there was pronounced lowering of the acid 3 months after the irradiation as compared with the pre irradiation levels

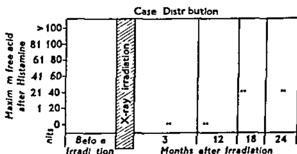


Fig 26 *The effect of X ray irradiation on gast ic secretion* 2000 r gastric tissue doses were gi en over a period of 3 weeks to lower the gastric secretion in cases of duodenal ulcer p eviously treated by antroduodenectomy with resection of the ulcer It will be noted that after an initial depression some cases showed a return of acid secretion

One year after the irradiation and later higher levels were reached in many of the cases while a few remained achlorhydric Serial gastric biopsies on a limited number of cases showed there was a corresponding change in the histology of the gastric mucosa (Brown G *et al* 1952 Brown G and Wood I J 1955)

The following case history illustrates the possibility of gastritis being caused by X ray irradiation A nurse aged 26 years de veloped *considerable flatulent dyspepsia and occasional vomiting*

and most probably has preceded the cancer (fig 28) However it may well be that the cancer came first and this caused an extensive zonal gastritis Possibly this was made worse by the malnutrition which results from the anorexia and dyspepsia of cancer Joske *et al* (1955) found normal mucosa in only 4 of 20 cases of cancer of the stomach examined by random biopsy



Fig 28 *Epithelial metaplasia in chronic gastritis* Gastric biopsy from a male patient aged 61 years known to have chronic atrophic gastritis for 10 years There is an unusual type of metaplasia of the epithelium with the down growth of irregular tubules lined by tall hyperplastic or atrophic epithelium There is a local inflammatory infiltration The patient is being closely observed for development of carcinoma (eosin and haematoxylin × 150)

Fairley *et al* (1955) surveyed 32 patients who for 5 years or more had been shown by gastric biopsy and other examinations to have uncomplicated chronic gastritis During the period of follow up serial tests were made including test meal gastric biopsy and barium meal The gastric biopsies showed little overall change during the period of observation the pronounced atrophic gastritis persisting with some fluctuation in the cellular infiltration There was a corresponding persistence in the depletion of acid secretion 24 of 32 showing either a fall or no change in free acid concentration and the remaining 8 a minor rise No patient in this group showed evidence of gastric cancer either during the period of

It is most improbable that duodenal ulcer would occur in the presence of an extensive gastritis owing to the lowered acid and pepsin secretion which results from the gastritis However on rare occasions gastritis may develop long after a duodenal ulcer has entered the chronic irreversible stage with penetration into the pancreas The anomalous position may then be found where a duodenal ulcer is associated with achlorhydria Probably most duodenal ulcers heal spontaneously after the development of extensive gastritis

A similar set of circumstances is provided artificially when gastritis is produced by X ray irradiation of the stomach (*vide supra*) This may lead to healing of the duodenal ulcer



Fig 27 *Zonal gastritis* The edge of a gastric ulcer showing zonal gastritis The lymph follicles are increased in number and size and the glands have almost completely disappeared There is dense submucosal fibrosis Ulceration is evident (lower right) (eosin and haematoxylin × 40)

Relationship of chronic gastritis to carcinoma

It has been debated over the years whether chronic gastritis favours the development of cancer It is known that cancer of the stomach especially when situated in the body of the stomach is usually accompanied by hypochlorhydria often achlorhydria It could therefore be concluded that extensive gastritis is present

reduction in the secretion of intrinsic factor the most significant results being obtained by studying the absorption of ^{58}cobalt labelled vitamin B_{12} the addition of intrinsic factor returning the absorption to normal Using our gastric biopsy tube they found atrophic gastritis in 41 of 50 patients with iron deficiency anaemia 2 further cases having gastric atrophy Davidson and Markson (1955) had similar results

Witts (1956) concluded that gastritis and achlorhydria are the direct result of iron deficiency

Joske *et al* (1955) carried out gastric biopsy in 11 patients with hypochromic microcytic anaemia who were not showing overt bleeding and 6 showed atrophic gastritis 3 superficial gastritis and the remaining 2 were within normal limits They concluded the achlorhydria so frequently seen in this type of anaemia results from inflammatory gastritis

Absorption of iron from alimentary canal Using foods containing radioactive iron Moore (1955) showed that absorption of iron was normal in patients suffering from iron deficiency anaemia and achlorhydria It is most probable that the majority of his subjects had atrophic gastritis Moreover he demonstrated that the addition of liberal volumes of dilute hydrochloric acid did not increase the absorption

TABLE 2 *Absorption of iron*

Cases of hypochromic anaemia (probably associated with chronic atrophic gastritis and anaemia) can absorb liberal amounts of iron given by mouth However cases showing the malabsorption syndrome with steatorrhoea show grossly impaired absorption

Authority	Test dose of ferrous iron given by mouth	Disease state	% Iron absorbed
Dubach *et al* (1948)	1 mg /kilo body weight	Normal subjects Hypochromic anaemia	2–21 4–71
Badenoch and Callender (1954)	40 mg	Hypochromic anaemia Steatorrhoea and hypochromic anaemia	20+ 0–3

observation or at the final assessment In addition there were 9 cases of atrophic gastritis who died before the 5 year period had passed and none had gastric cancer Although the number of patients in this study is limited it does not support the opinion that chronic gastritis strongly favours the development of cancer

If atrophic gastritis is not a precursor of cancer it would suggest that the causal factor of gastritis is not carcinogenic However in this regard one would not readily care to discard the thought that X rays could act as a carcinogen (Brown and Wood 1956) Indeed Levin and his colleagues (1957) in a follow up of 723 patients treated by irradiation for duodenal ulcer reported 6 to have died from carcinoma of the stomach duodenum or pancreas 2–13 years after irradiation They considered that the significance of this is yet to be determined

Witts (1956) who had studied cases of achlorhydria atrophic gastritis and hypochromic anaemia for many years could find no reliable data on the liability of women with iron deficiency and achlorhydria to develop carcinoma of the stomach in later life He concluded we know that they are abnormally prone to develop carcinoma of the mouth and hypopharynx and we should keep an open mind about the liability to carcinoma of the stomach Fig 28 is of interest in this regard

Relationship of chronic gastritis to anaemia

When anaemia does occur in cases of chronic atrophic gastritis it is usually of the iron deficiency type being hypochromic and microcytic Several factors contribute to this anorexia leads to a depleted intake of food and the food taken is often low in iron and protein content secondly it has been claimed that there may be impaired absorption of iron due to greatly reduced secretion of acid by the stomach thirdly there may be repeated gastric haemorrhages due to excessive shedding of gastric epithelium the haemorrhage usually being minimal but oft repeated and lastly with increasing atrophy of the gastric mucosa the supply of intrinsic factor may be reduced causing impaired absorption of vitamin B_1 *and ultimately pernicious anaemia (see Chapter 5)*

Witts anaemia Witts (1956) found that the incidence of achlorhydria is increased at all ages amongst cases of iron deficiency anaemia—under 50 years it was 4 times as common as in a control group He and his colleagues at Oxford also found a

medical treatment (fig 29) However the blood loss in gastritis is usually occult although it may lead to pronounced anaemia

Treatment

Since most patients with chronic gastritis suffer minor bouts of discomfort they only require simple treatment during the attacks We found that alkaline powders provided the greatest relief odd though this may seem in the light of the achlorhydria It is of course rational to administer dilute hydrochloric acid with meals, but few claim benefit from this and actually most are made more uncomfortable However there were exceptions to this experience for a few patients obtained considerable benefit from the acid

Should the relapse be moderately severe and prolonged oral penicillin may be given with benefit—100 000 units 4 hourly for 10 days *There is evidence that penicillin is absorbed through* normal gastric mucosa (Hurley and Bazeley 1957) but it is not known whether this pertains when chronic gastritis is present

When overt haemorrhage occurs with melaena or haematemesis the patient should be given rest in bed and placed on a haematemesis regime However rapid and severe blood loss requiring a liberal blood transfusion or gastrectomy rarely occurs

Should anaemia be present it is usually of the iron deficiency type and responds to iron given by mouth Ferrous sulphate is a satisfactory salt but should this cause added dyspepsia the other salts such as ferrous lactate or iron and ammonium citrate may be satisfactory Some patients are intolerant to all oral medication or the anaemia is not relieved owing to intestinal malabsorption (Table 2) In these an intramuscular preparation such as Imferon* (- ml twice a week) is of value Hagedorn (1957) has described a short high dosage course of this preparation

If the anaemia is not relieved by iron then further search should be made for blood loss or other causes of anaemia such as chronic nephritis (Joske *et al* 1956) or carcinoma of the colon It should be remembered that the atrophic gastritis may eventually cause progressively increasing vitamin B_1 deficiency from diminishing secretion of intrinsic factor – macrocytic anaemia will then appear This onset of pernicious anaemia will respond to injections of B_1

When chronic flatulent dyspepsia lack of appetite loss of weight and anaemia occur in an elderly patient as a result of

* Benger Laboratories Ltd Cheshire England

It will be noted in Table 2 that the absorption of iron from the alimentary canal is increased in iron deficiency anaemia unless this deficiency is associated with steatorrhoea when absorption is reduced. In steatorrhoea it is the intestinal barrier which is at fault for iron is readily absorbed and utilised when injected parenterally (Dubach *et al* 1948 Badenoch and Callender 1954)

It would appear probable that the most common causes of hypochromic anaemia associated with gastritis are deficiency of iron in the diet and loss of iron from chronic bleeding from the gastric mucosa (fig 29). Moreover it is considered that the iron deficiency follows the gastritis rather than causing it as has been claimed by Witts. Indeed the gastritis is one of the causes of the iron deficiency



Fig 29 *Chronic atrophic gastritis with haemorrhage* A male patient aged 38 years had periodic epigastric pain over a period of 5 years. Admitted with haematemesis and melaena. X-ray revealed no ulcer or cancer. The gastric biopsy performed 11 days after admission shows haemorrhagic infiltration of the *lamina propria*. The red cells stain darkly (trichrome stain × 150)

Overt bleeding In a study of 112 cases of gastritis diagnosed by gastric biopsy Doig and Wood (1952) described 4 cases of superficial gastritis and 3 of atrophic gastritis who had been admitted to hospital with haematemesis or melaena. No other cause for the bleeding such as ulcer or cancer was found and all recovered with

CHAPTER 4

DIFFUSE GIANT HYPERTROPHIC GASTRITIS

Since the earliest description of diffuse giant hypertrophic gastritis by Menetrier (1888) perusal of the literature shows that personal experience of this disease by any one author is restricted to only a few cases and we have encountered only one case to be described later Nevertheless Fieber (1955) has recorded an excellent analysis of 50 cases reported in the literature The lesion is traditionally regarded as inflammatory in origin but the aetiology is unknown It may be that the pathological changes seen in this disease are basically neoplastic an anatomical variant of gastric adenomatosis and that the inflammatory reaction is a secondary occurrence This view is favoured by the very prominent folds the profuse epithelial proliferation and the occasional development of true carcinoma (Matzner *et al* 1951 Palumbo *et al* 1951 Texter *et al* 1953)

The lesion may diffusely involve the whole gastric mucosa or it may be more localised in distribution particularly in the antrum The gastric mucosal folds are swollen tortuous nodular and even polypoid ranging from 0 5 to 3 5 cm in height The surface of the folds may be congested with a mammillary or cobblestone pattern superficial haemorrhages and erosions The mucosa is soft and usually mobile but may become more turgid and relatively fixed due to inflammatory induration or malignant change There may be a tendency for the redundant mucosa to prolapse through the pylorus

The *microscopic appearance* is basically that of benign hyperplasia of the surface epithelium resulting in extensive elongation, branching and tortuosity of the pits Cystic changes may become pronounced presumably the result of obstruction and inflammation in these pits There is infiltration of the interstitium by inflammatory cells Normal glands may be visible in the depth of the mucosa

chronic gastritis malignancy may well be suspected by both patient and physician Indeed it is essential first to exclude the presence of cancer in such a patient But once this has been done, the patient will profit greatly by having the disease entity chronic gastritis explained to him (or more frequently her) He should be reassured that his symptoms are typical of this malady and that there is no evidence of cancer Moreover, he will be comforted by the knowledge that although he may suffer a minor relapse from time to time he will enjoy good health and regain his weight with improved diet and medicinal treatment He should be seen from time to time to maintain treatment and to ensure accuracy of diagnosis

* * *

It is our opinion that the acceptance by physicians and surgeons of chronic gastritis as a real disease entity with specific symptoms and signs is essential to the efficient practice of medicine

Fig 30 *Diffuse giant hypertrophic gastritis* Operative specimen of stomach There is pronounced thickening tortuosity and mammillation of the rugae of the body of the stomach The antrum (left) is normal The patient was a male aged 47 years with epigastric pain and recurrent haematemesis for 2 years A pre operative diagnosis of carcinoma of the stomach was made in error (approximately half natural size)



Fig 31 *Diffuse giant hypertrophic gastritis* Microscopic appearance of the gastric mucosa (see fig 30) There is gross proliferation and cystic change in the pits The interstitial tissue is heavily infiltrated with inflammatory cells (eosin and haematoxylin ×45)

Fieber (1955) found that diffuse giant hypertrophic gastritis occurred in adults of all ages but particularly in the fourth to sixth decades of life Males outnumbered females by 3 1 The average duration of symptoms was 2 years and these included in order of frequency diffuse post prandial epigastric pain and tenderness sometimes relieved by food and alkalis weight loss vomiting and bleeding Test meal findings were not characteristic The large rugae were detected by gastroscopy and barium meal examination

The differential diagnosis at this stage is from (1) malignant neoplasms of the stomach notably carcinoma (most frequent misdiagnosis) sarcoma and reticulosis (2) benign neoplasms of the stomach (3) large gastric rugae especially in the deflated stomach (Ricketts *et al* 1947) (4) granulomata of the stomach (5) extrinsic tumours invading the stomach

Biopsy through the gastroscope cytological studies and blind biopsy with the flexible gastric biopsy tube may be of value in differentiating between these conditions but a reliable diagnosis of diffuse giant hypertrophic gastritis can only be made by the pathologist with access to the full thickness of the stomach wall at any area he may wish to examine Cases in which there is any suspicion of a resectable malignancy should be submitted to laparotomy

Stiegmann *et al* (1957) consider the following features suggest that the large rugae are benign a long history response to medical treatment absence of a palpable mass normal or near normal test meal a smooth outline of the filling defect elasticity of the under lying gastric wall smoothness and continuity of the rugae and decrease in the size of the lesion during observation Such a case they suggest may undergo conservative treatment and observa tion but generally the resemblance of diffuse giant hypertrophic gastritis to carcinoma leads to laparotomy

Fieber (1955) states that the response to medical regimes or deep X ray therapy is not good Where there is suspicion of malignancy and the lesion is diffuse total gastrectomy is necessary but if the lesion is proven to be benign at operation subtotal gastrectomy suffices even though the lesion is diffuse

Case history We are indebted to Dr W E King for the follow ing case record A male patient aged 42 years was admitted to hospital with a history of indigestion for 10 years and during the past year a haematemesis followed by tiredness malaise and epigastric pain A barium meal examination showed an extensive

CHAPTER 5

GASTRIC ATROPHY, PERNICIOUS ANAEMIA AND SUBACUTE COMBINED DEGENERATION OF THE CORD

Structural changes of gastric atrophy and pernicious anaemia

In 1849 Thomas Addison presented his classical description of the anaemia which for many years bore his name It was in 1860 however, that Flint drew attention to the gross reduction of gastric secretion in Addisonian anaemia and Cohn and von Mering (1866) noted the absence of hydrochloric acid from the gastric juice The gastric atrophy accompanying this condition was first noted by Samuel Fenwick (1870) who subsequently confirmed this finding in 3 other cases (Fenwick 1880) Faber (1935) considered the changes in the stomach were inflammatory in origin and that gastric atrophy was the end result of this process but Magnus and Ungley (1938) described a non inflammatory atrophy of the body of the stomach in 8 patients with pernicious anaemia Similar observations were also made by Meulengracht (1939) and Cox (1943)

The macroscopic appearances described by these authors are characteristic of gastric atrophy The mucosa of the body of the stomach is reduced in thickness and the atrophy also includes the muscle coats By contrast the pyloric mucosa and muscle coat are normal in appearance the demarcation between the two areas being quite sharp (fig 32)

The histological changes in the mucosa of the body of the stomach as recorded by these authors resemble the gastric atrophy described in the gastric biopsies by Motteram (1951) of our unit These changes are the virtual disappearance of the parietal and chief cells of the glands with partial replacement by areas showing intestinal metaplasia and non specific secreting cells while inflammatory changes are minimal or absent (fig 6) In 90 per cent of cases all the specific cells of the glands have disappeared while

filling defect suggestive of carcinoma of the stomach At gastroscopy thickened folds suggestive of carcinoma were seen projecting into the stomach Total gastrectomy was performed by Mr J O Smith The post operative recovery was slow and he continued to suffer from dyspepsia The pathologist Dr J D Hicks reported that the stomach measured 23 cm along the lesser curvature the mucosa was pink hypertrophied and heaped up into numbers of large papillary folds the whole of the mucosa having a gross mammillary appearance (fig 30) On microscopic examination the epithelium of the mucosal folds was in many places normally differentiated but contained numerous plasma cells in the outer portion of the mucosa and many lymphocytes in the basal portion (fig 31) Also there were cystic glands in the lower portion of the mucosa and in some areas these were well differentiated Some dilated glands extended into the submucosa and were lined by regular mucus secreting cell

Motteram 1950 Doig Motteram Robertson and Wood 1950 Motteram 1951 Wood 1951 Finckh and Wood 1953 Badenoch and Richards 1953 Doig 1954 Badenoch 1954) In practice a continuous range of histology is encountered from atrophic gastritis to gastric atrophy so that it is possible that many cases of gastric atrophy are in fact the inactive end result of a severe atrophic gastritis Conversely cases of gastric atrophy from time to time may develop superimposed inflammatory changes For the purposes of classifying and analysing our biopsy results we have used the criteria set out in Table 3

TABLE 3 *The histological changes in atrophic gastritis and gastric atrophy*

Biopsy examination	Atrophic gastritis	Gastric atrophy
Disappearance of gland cells	Usually incomplete	Usually complete
Intestinal metaplasia	Uncommon and is patchy and often confined to the pits	Usually present and tends to be diffuse
Inflammatory changes	Epithelial irregularity cellular infiltration including polymorphs increase in *lamina propria* thickened and splintered *muscularis mucosae* all pronounced	Usually mild or absent with only superficial changes

Of 1000 gastric biopsies reviewed in 1955 by Joske Finckh and Wood 100 were obtained from patients with either pernicious anaemia or subacute combined degeneration of the cord or both Gastric atrophy was present in 40 and in the remaining 60 there were varying degrees of chronic gastritis with severe atrophy All of the 100 patients had histamine fast achlorhydria These authors also found gastric atrophy in 16 biopsies from patients without overt pernicious anaemia or subacute combined degeneration of the cord One of these subsequently developed macrocytic anaemia and subacute combined degeneration of the cord which responded to treatment with vitamin B_{12} (Robertson Wood and Joske 1955) (*vide infra*) Three of the other biopsies were obtained from patients who at other times showed atrophic gastritis illustrating both the relationship between these conditions

an occasional chief cell may be found in the others Parietal cells are rarely seen Intestinal metaplasia is usually present and diffusely distributed in the mucosa the superficial epithelium consisting of columnar cells with a dark border goblet cells and argentaffin cells while Paneth cells are present in the bases of the crypts Gastric type epithelium when present stains intensely for mucin The superficial epithelium is regular and the *muscularis mucosae* is thin The *lamina propria* is slightly increased and often contains a few plasma cells and lymphocytes the latter occasionally aggregated into small follicles at the base of the mucosa The average width of the processed mucosa in this condition is 0 42 mm the average normal being 0 54 mm (Joske *et al* 1955)



Fig 32 *Gastric atrophy* A male aged 58 years with severe pernicious anaemia died immediately after admission to hospital from anaemia bronchopneumonia and cardiac failure There is gross atrophy of the mucosa of the body of the stomach The antrum and pylorus (left) appear normal (approximately half natural size)

It cannot be stated however that the morphological changes in the stomach found in cases of pernicious anaemia and subacute combined degeneration of the cord are uniform except in so far as most authors now agree that atrophy with or without inflammation of the mucosa of the body of the stomach is invariable and usually severe (Doig 1949 Doig and Wood 1950 Doig and

gastric biopsies and maximum stimulus histamine test meals over a period of 8 years (fig 33) With treatment he made the usual complete clinical recovery and then remained well on maintenance treatment first with liver extract and then liberal doses of vitamin B_{12} but gastric atrophy and achlorhydria persisted throughout (Finckh and Wood 1953)

Symptomatology of gastric atrophy and pernicious anaemia

Much depends on the sequence of events which leads to gastric atrophy If gastric atrophy is a slow primary atrophy of the mucosa probably genetically determined and unaccompanied by an inflammatory reaction (gastritis) then the gastric symptoms will usually be minimal or absent and the clinical picture will be dominated by varying degrees of vitamin B_{12} deficiency with anaemia and subacute *combined degeneration* of the cord If however the advent of vitamin B_1 deficiency is preceded by severe chronic gastritis slowly progressing from the stage of superficial gastritis to atrophic gastritis and perhaps thence to gastric atrophy then it might be expected that there would be a long history of intermittent flatulent dyspepsia typical of gastritis

Analysis of the symptoms before the appearance of overt pernicious anaemia is therefore of considerable interest

Most cases of pernicious anaemia enjoy excellent health without dyspeptic symptoms once adequate vitamin B_{12} therapy has been established Thus the gastric atrophy *per se* produces few symp toms On the other hand some patients first presenting with the pernicious anaemia picture complain of sore tongue poor appetite mild to moderate flatulent dyspepsia general malaise and perhaps bouts of diarrhoea Most of this can be attributed to vitamin B_{12} deficiency and not to gastric atrophy and the resulting achlorhydria

The male patient aged 65 years previously reported by Robert son Wood and Joske (1955) is of considerable interest in this regard When seen in February 1949 he stated that he had suffered from flatulent dyspepsia since the age of 15 The pain came on soon after taking food and was relieved by belching or taking alkaline powders His appetite was poor and he had lost weight He was referred to the hospital with the provisional diagnosis of gastric carcinoma but this was excluded by X ray and gastroscopy Investigation showed that he had achlorhydria gastric atrophy (repeated biopsies) normal bone marrow and

and the difficulty of completely separating them on histological grounds

Following the administration of vitamin B_{12} to cases of pernicious anaemia there is no change in the appearance of the gastric biopsy (Doig and Wood 1950 Finckh and Wood 1953) We have not been able to observe a change in the size of the epithelial cells which would be in accord with the findings of Graham and Rheault (1954) who reported large gastric epithelial cells in gastric washings comparable to the megaloblasts in the bone marrow and which returned to normal size with vitamin B_{12} therapy Also Massey and Rubin (1954) and Gamble *et al* (1957) noted no significant change in the size of the epithelial cells in gastric washings following vitamin B_{12} therapy



Fig 33 *Gastric atrophy* A male aged 47 years with pernicious anaemia treated with liver extract and then vitamin B_{12} for 8 years The gastric biopsy shows diffuse intestinal metaplasia and complete atrophy of the gland There is slight infiltration of the *lamina propria* with plasma cells and lymphocytes Serial gastric biopsies taken before and during treatment have shown no change in the histological appearance (mucicarmine × 150)

In our experience the gastric atrophy and the resulting achlorhydria remain unchanged even after many years of full parental vitamin B_{12} therapy One such patient a male chocolate maker aged 47 years suffering from pernicious anaemia and subacute combined degeneration of the cord has been studied by serial

cord in the absence of any abnormality in the peripheral blood or bone marrow may present a considerable problem in diagnosis (Victor and Lear, 1956) (figs 34 35) It is odd that vitamin B_{12} deficiency causes such a variable clinical picture varying from severe anaemia with no overt subacute combined degeneration of the cord to severe combined cord degeneration and no anaemia In our present state of knowledge we can but believe that there is a different degree of system vulnerability varying from patient to patient However histamine fast achlorhydria is always present and gastric biopsy reveals a severe degree of atrophy of the gastric mucosa (Doig *et al* 1950A)



Fig 34 *Severe active chronic atrophic gastritis* A male patient aged 64 years was admitted with weakness in the legs and evidence of posterior and lateral column degeneration in the spinal cord There was a histamine fast achlorhydria but peripheral blood and bone marrow were normal The gastric biopsy shows irregularity and shedding of the superficial epithelium pseudopyloric metaplasia and complete loss of parietal and chief cells of the glands The *lamina propria* is infiltrated with inflammatory cells and the *muscularis mucosae* is thickened and splintered There was a good response to vitamin B_{12} therapy (eosin and haematoxylin × 150)

*Cobalt labelled vitamin B_{12} has been used to detect impaired vitamin B_{12} absorption in this syndrome (McIntyre *et al* 1956) Liversedge *et al* (1957) found radioactive vitamin B_{12} of considerable help in confirming doubtful cases of subacute combined

peripheral blood and only very minor signs suggestive of subacute combined degeneration of the cord The technique for estimating serum B_{12} levels was not then available He was not given vitamin B_{12} treatment as he was enjoying quite good health and he improved with reassurance and a more satisfactory diet However he was kept under close observation and in September 1954 he developed overt pernicious anaemia with pronounced subacute combined degeneration of the cord and a low level of serum vitamin B_{1} There was a full response to liberal vitamin B_{1} and he was well controlled by continuing therapy When last seen nearly 4 years later he was enjoying excellent health but still suffered from some flatulent dyspepsia Examination of his blood and nervous system were satisfactory there was achlorhydria to maximum histamine stimulation covered by antihistamine (Kay 1953) and gastric biopsy showed the same picture of gastric atrophy

A similar delay in the development of overt pernicious anaemia after depleted vitamin B_{1} absorption from intrinsic factor lack may be observed in patients subjected to total gastrectomy Here the onset of symptoms may be delayed for periods up to 3 years or more after the gastrectomy the patient meanwhile subsisting on the body stores of vitamin B_{12} (Welbourn *et al* 1956 Harvey 1956)

Recently Holmes (1956) has stressed the mental changes which accompany pernicious anaemia and which he attributes not only to cerebral anoxia but also to the effect of vitamin B_{1} deficiency *on the brain for the symptoms may be present before anaemia* and subacute combined degeneration of the cord appear Moreover they are relieved by vitamin B_{1} therapy

Wilkinson (1948) reported flatulence or dyspepsia in 59 per cent of cases of pernicious anaemia and the symptoms often antedated the anaemia by many years Davidson (1957) noted that poor appetite and vague abdominal discomfort were frequent in pernicious anaemia but diarrhoea only occurred in 9 per cent of 250 cases which he reviewed in Edinburgh during 1944–56 He contrasted this finding with Cabot s series of 1200 cases seen before the discovery of liver therapy where the incidence of diarrhoea was 51 per cent

It may well be that vitamin B_{12} deficiency directly impairs gastric and intestinal function and this is remedied by vitamin B_{12} therapy

The development of subacute combined degeneration of the

severe atrophy of the gastric mucosa so the cause of this atrophy must be sought when determining the cause of pernicious anaemia

Since gastric biopsy examinations were first made in our unit in 1948 we have made a number of studies of pernicious anaemia

In 1950 Doig and Wood examined by gastric biopsy 45 cases of established pernicious anaemia or subacute combined degeneration of the cord and more recently Joske Finckh and Wood (1955) have extended the series to 100 cases All had severe gastric changes with atrophy 40 were classified as gastric atrophy no signs of inflammation being present and 60 had varying degrees of chronic gastritis with severe atrophy All had histamine fast achlorhydria

In Scotland Markson and Davidson (1956) carried out gastric biopsy in 16 cases of pernicious anaemia and found gastric atrophy in 14 and atrophic gastritis in 2

It is rational to conclude that severe atrophic gastritis may lead to gastric atrophy with subsidence of the inflammatory reaction and that the causes of pernicious anaemia thus include the causes of superficial gastritis which then progresses to atrophic gastritis (see Chapter 4) This progression probably takes a number of years and so far our 8 year study of gastritis has not produced an example of the complete progression through the 3 phases We have seen some cases of superficial gastritis progressing to atrophic gastritis and some cases of severe atrophic gastritis progressing to gastric atrophy but without the development of overt pernicious anaemia or subacute combined degeneration of the cord These may appear later with depletion of the vitamin B_{12} stores

There is also evidence that gastric atrophy may occur as a primary process a simple abiotrophy of the gastric mucosa without a preceding inflammatory gastritis (Magnus and Ungley 1938 Motteram 1951) It may well be that there is a genetic influence in this primary degeneration It is therefore of importance that the occurrence of pernicious anaemia in families has been reported by a number of writers Wilkinson (1949) investigated 1600 cases of pernicious anaemia and found a history of pernicious anaemia in at least one other member of the family in 19 per cent Mosbeck (1953) investigated 132 patients with pernicious anaemia in whom a relatively complete family history could be obtained There were 1958 relatives with 51 (2 3 per cent) cases of pernicious anaemia this was 20 times that found in a control series More over 30 per cent of the families had one or more cases additional to the index case

degeneration of the cord either when there was no accompanying anaemia or when vitamin B_{12} had been given before the blood state had been adequately examined

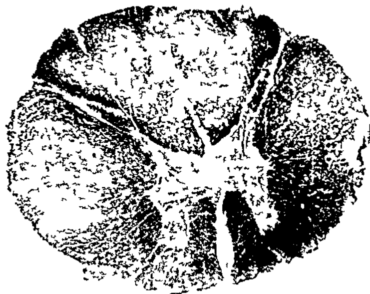


Fig 35 *Subacute combined degeneration of the cord* A female patient aged 64 years developed urinary retention and progressive weakness of the legs over 2 weeks She had a smooth tongue wasting of the leg muscles with absent deep reflexes extensor plantar responses and loss of sensation to light touch pinprick and vibration over both legs Gastric biopsy sho ed gastric atrophy She died of urinary sepsis 6 weeks later despite injections of liver extract and antibiotics A section of the lumbar portion of the spinal cord shows extensive demyelina t on of the posterior and lateral columns (Weigert stain × 20)

Aetiology of gastric atrophy and pernicious anaemia

It is of considerable importance to speculate as to the cause of pernicious anaemia As will be discussed later it must be accepted that pernicious anaemia is due to impaired vitamin B_{12} absorption which in turn is due to deficiency of Castle s intrinsic factor This intrinsic factor is present in the mucoprotein fraction of gastric juice Some patients may also secrete intrinsic factor in the duo denum and perhaps the upper ileum but in relatively minimal amounts (Castle *et al* 1929 Grasbeck 1956) In pernicious anaemia the cause of the deficiency of Castle s intrinsic factor is

of 18 patients with severe atrophy of the mucosa had a low total volume of secretion achlorhydria and low or absent pepsin while all of 36 patients with normal or nearly normal mucosa had normal or intermediate type secretions (Wood *et al* 1949B) Similarly the total mucus secretion was reduced in chronic gastritis and more so in gastric atrophy even though the mucus was more concentrated (Weiden 1949)

In a later survey Joske *et al* (1955) recorded 784 gastric biopsies in patients who had also been examined by histamine test meal (see fig 1 Chapter 1) The test meal yielded a concentration of over 20 units of free acid in 76 per cent of 275 biopsies which were within normal limits in only 15 per cent of 172 showing pronounced atrophic gastritis and in none of 41 showing gastric atrophy

In 1929 Castle and his co workers demonstrated that an intrinsic factor present in normal human gastric juice combined with the food to produce a haemopoietic response when given orally to patients with pernicious anaemia

The localisation of the intrinsic factor in the pylorus and duodenum of the pig was achieved by Meulengracht (1939) but Fox and Castle (1942) demonstrated that in man this factor was present mainly in the body of the human stomach so that the gastric lesion could be correlated with the absence of intrinsic factor Goldhamer (1937) had shown that the gastric juice of patients with pernicious anaemia contained minute amounts of intrinsic factor but because of the achylia he suggested that the defect was mainly quantitative

Intrinsic factor has since been identified as a mucopolypeptide (Williams *et al* 1954) present in the mucoprotein of gastric juice (Latner *et al* 1954) It now seems likely that intrinsic factor combines with extrinsic factor (vitamin B_1 or cyanocobalamin isolated by Smith 1948 and Rickes *et al* 1948) and facilitates its absorption in the small intestine (Ross 19 0) It is stored in the liver combined to a beta globulin (Pitney *et al* 1955) and then combined to an alpha globulin (Pitney *et al* 1954) it is transported in the plasma to the sites of utilisation In conjunction with folic acid vitamin B_1 is thought to play a major role in the synthesis of nucleoprotein particularly at the sites of rapid cell proliferation such as the bone marrow Vitamin B_1 deficiency occurring as a result of deficiency of intrinsic factor is followed by a decrease in the rate of cellular proliferation The cells instead of dividing

It is also of interest that Videbaek and Mosbech (1954) found gastric carcinoma to be 4 times higher in the relatives of patients with gastric carcinoma than in a control series and that in their series the incidence of pernicious anaemia was about 3 times higher than the normal in the relatives of patients with gastric carcinoma a finding which accords with the treble incidence of gastric carcinoma in patients with pernicious anaemia They concluded changes in the gastric wall—which presumably may be the result of exogenous as well as hereditary factors—therefore appear to predispose to both gastric carcinoma and pernicious anaemia

Doig *et al* (1950B) carried out histamine test meals on 134 healthy medical students and found only one with histamine fast achlorhydria This student a male aged 25 had no signs of pernicious anaemia and the barium meal X ray was negative Gastric biopsy in 1949 showed an unusual type of atrophy of the acid and pepsin secreting cells and an absence of inflammation His maternal grandmother had died at the age of 70 from pernicious anaemia His mother at the age of 44 suffered from flatulent dyspepsia and weakness and a gruel meal showed hypochlorhydria and excess mucus In 1955 histamine fast achlorhydria was still present and in 1957 when last seen he was well and had required no treatment

In conclusion it can be stated that there is evidence that a proportion of the cases of pernicious anaemia result from a primary atrophy of the gastric mucosa which may begin early in life and *be determined by a genetic factor* The extent of the atrophy may not be sufficient to produce vitamin B_{12} deficiency and pernicious anaemia till middle age or later Secondly the remaining cases of pernicious anaemia probably result from superficial gastritis progressing to severe atrophic gastritis with resulting depletion of Castle s intrinsic factor which in turn leads to *depleted vitamin B_{12} absorption and vitamin B_{12} deficiency* This atrophic gastritis may become quiescent with disappearance of the inflammatory reaction in the gastric mucosa and so the gastric biopsy finding is that of gastric atrophy

The relationship of the gastric changes to pernicious anaemia subacute combined degeneration of the cord and other megaloblastic anaemias

In a correlation of the gastric secretions obtained by histamine test meal with the findings on gastric biopsy it was found that all

of 18 patients with severe atrophy of the mucosa had a low total volume of secretion achlorhydria and low or absent pepsin while all of 36 patients with normal or nearly normal mucosa had normal or intermediate type secretions (Wood *et al* 1949B) Similarly the total mucus secretion was reduced in chronic gastritis and more so in gastric atrophy even though the mucus was more concentrated (Weiden 1949)

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and maturing become larger and remain immature, giving rise to megaloblasts

Vitamin B_{12} is stored in the liver in liberal amounts and its utilisation is slow Thus when the absorption from the alimentary canal is retarded or ceases completely there is a delay in the development of overt pernicious anaemia or subacute combined degeneration of the cord As stated previously this is demonstrated after total gastrectomy when it may take several years for megaloblastic anaemia to develop

The relationship of vitamin B_1 deficiency to the demyelinating peripheral neuritis and subacute combined degeneration of the cord is obscure The lesions have been attributed to defective ribose nucleic acid synthesis affecting especially the long axones of nerve cells in the spinal cord (Nieweg *et al* 1954)

Can pernicious anaemia be diagnosed in the presence of normal acid secretion and normal appearance of the gastric biopsy?

Mollin *et al* (1955) presented a case of pernicious anaemia without gastric atrophy This case was initially diagnosed at the age of 13 months The father of this patient subsequently developed an early pernicious anaemia which was associated with gastric atrophy The mother had a brother who died of carcinoma of the stomach when aged 30 years Moreover it is of considerable interest that the mother and father were cousins as consanguinity greatly enhances genetic influences It was suggested that the early development of pernicious anaemia in the propositor was genetically determined the patient being homozygous with respect to the faulty gene It was also suggested that the early treatment of the case prevented the development of gastric atrophy and that gastric atrophy was in fact secondary to prolonged vitamin B_1 deficiency which might be clinically silent for a long period Similarly Harris Jones *et al* (1957) reported pernicious anaemia without gastric atrophy in a girl of 16 years

Pernicious anaemia is very rare in children but Reisner *et al* (1951) found 5 cases in the literature in which hydrochloric acid was found in the gastric juice and they described 3 further cases in which there was hydrochloric acid in the gastric juice at some stage This suggests that in the pernicious anaemia of

childhood achlorhydria is not so constant and that presumably the gastric atrophy is either absent or incomplete

This finding is consistent with the concept of Mollin and his colleagues but it must be emphasized that such cases are at most rarely found —in classical pernicious anaemia the atrophic changes in the gastric mucosa are severe and achlorhydria is present

Indeed we have not seen a case of pernicious anaemia without gross atrophy of the gastric mucosa and achlorhydria Like Witts (1956) we *wish to reserve judgment on the cases in this* group We do not consider they should be diagnosed as suffering from pernicious anaemia

Definition of "pernicious anaemia'

It is of interest that Davis and Brown (1953) defined pernicious anaemia as a megaloblastic anaemia with irreversible degeneration of the gastric mucosa Witts (1956) stated the final argument for the priority of gastric atrophy in the development of pernicious anaemia is the complete failure to reverse the atrophy and achylia by vitamin B_{12} or any other therapeutic agent In our present state of knowledge we agree with Witts

Treatment of gastric atrophy, pernicious anaemia and subacute combined degeneration of the cord

Once the diagnosis *of pernicious anaemia or subacute combined* degeneration of the cord is established intramuscular injections of vitamin B_{12} should be given Before overt macrocytic anaemia or subacute combined degeneration of the cord appear there is a gradual depletion of the vitamin B_{12} stores especially in the liver so that when treatment is begun these stores should be rapidly and fully replenished It is wise to give 1000 micrograms of vitamin B_{12} every second day for the first week and then weekly for 2 months Iron also may be required to restore the normal blood picture After 2 months liberal treatment with vitamin B_{12} smaller doses of 100 micrograms can be given every 3–4 weeks to maintain adequately the erythrocyte count and haemoglobin level A few patients appear to require 200 micrograms or more but once vitamin B_{12} fails to control the anaemia other causes should be sought especially cancer of the stomach or bowel or chronic renal disease

Should the initial anaemia be profound and the patient's life threatened and especially if there be an accompanying infection such as pneumonia then a blood transfusion can be life saving The blood should be carefully matched and cross typed for transfusion reactions are frequently encountered in these patients The use of packed cells to avoid overloading of the circulation with plasma should be considered However most cases can be restored to health with liberal doses of vitamin B_1 and appropriate antibiotics without resorting to transfusion

Throughout the present studies full doses of parental vitamin B_1 *have been employed Preparations for oral administration* containing both B_{12} and intrinsic factor in the form of animal (heterologous) mucosal extract have been disappointing in that their potency may wane after the passage of months or years Schwartz and Meulengracht (1957) have attributed this fall in potency to the development of antibodies to heterologous extract They demonstrated human (autologous) gastric mucosal extract to be still efficient when the animal extract was failing

The treatment of patients with severe subacute combined degeneration of the cord with or without accompanying pernicious anaemia requires the same initial liberal dosage of vitamin B_1 It has been claimed that with continued high dosage good results are obtained All patients show improvement but in severe cases the recovery is incomplete Moreover should the residual weakness be pronounced it may increase with advancing years probably due to failing blood supply from progressive atherosclerosis

It has already been emphasised that the gastric lesion in classical pernicious anaemia and subacute combined degeneration of the cord is irreversible despite long continued therapy with liver *preparations (Doig and Wood 1950 Wilkinson 1949) and* with vitamin B_1 (Finckh and Wood 1953) Thus gastric biopsy is of value in reviewing the diagnosis in patients who have received some previous treatment with liver or vitamin B_{12} It is also of value in the diagnosis of pernicious anaemia as opposed to other types *of megaloblastic anaemia in which severe gastritis or gastric* atrophy may not occur namely those due to dietetic deficiency intestinal malabsorption liver disease and drugs such as Epanutin * (Badenoch 1954)

Delay in the diagnosis and treatment of subacute combined degeneration of the cord may *result either from failure to recognise*

* Epanutin (sodium phenytoin) Parke Davis

the significance of the peripheral dysaesthesiae which may precede other manifestations by many months or from a reluctance to diagnose this condition in the absence of the characteristic haematological abnormalities Here gastric biopsy has been a most valuable aid in making an early diagnosis (Doig Motteram Robertson and Wood 1950A) The serum vitamin B_1 estimations and radioactive vitamin B_1 absorption tests are also proving to be of considerable value

Alcoholic peripheral neuritis associated with chronic atrophic gastritis and histamine fast achlorhydria may simulate early sub-acute combined degeneration of the cord

EPILOGUE

And what of the future?

In the light of experience in our unit and elsewhere will gastritis become a widely accepted malady sympathetically managed by the attending physician? Will the atomic age with increasing exposure to radiation produce more sufferers from chronic atrophic gastritis? Will this in turn lead to more cases of pernicious anaemia? And more cases of gastric cancer? And fewer cases of duodenal ulcer? What will be the future of alcoholism—will it be successfully controlled by social reform? And what will be the final assessment of the effect on the gastric mucosa of the stress reactions of Selye and of Wolf and Wolff?

Let us look into the future and encourage our successors to study man and his way of life in this changing world It will be of particular interest to gastroenterologists to observe the impact of man s way of life on the structure and function of the gastric mucosa

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